The American Journal of Medicine

Symposium on Aviation Medicine

Guest Editor

JAN H. TILLISCH, M. D.

May 1948

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The American Journal of Medicine

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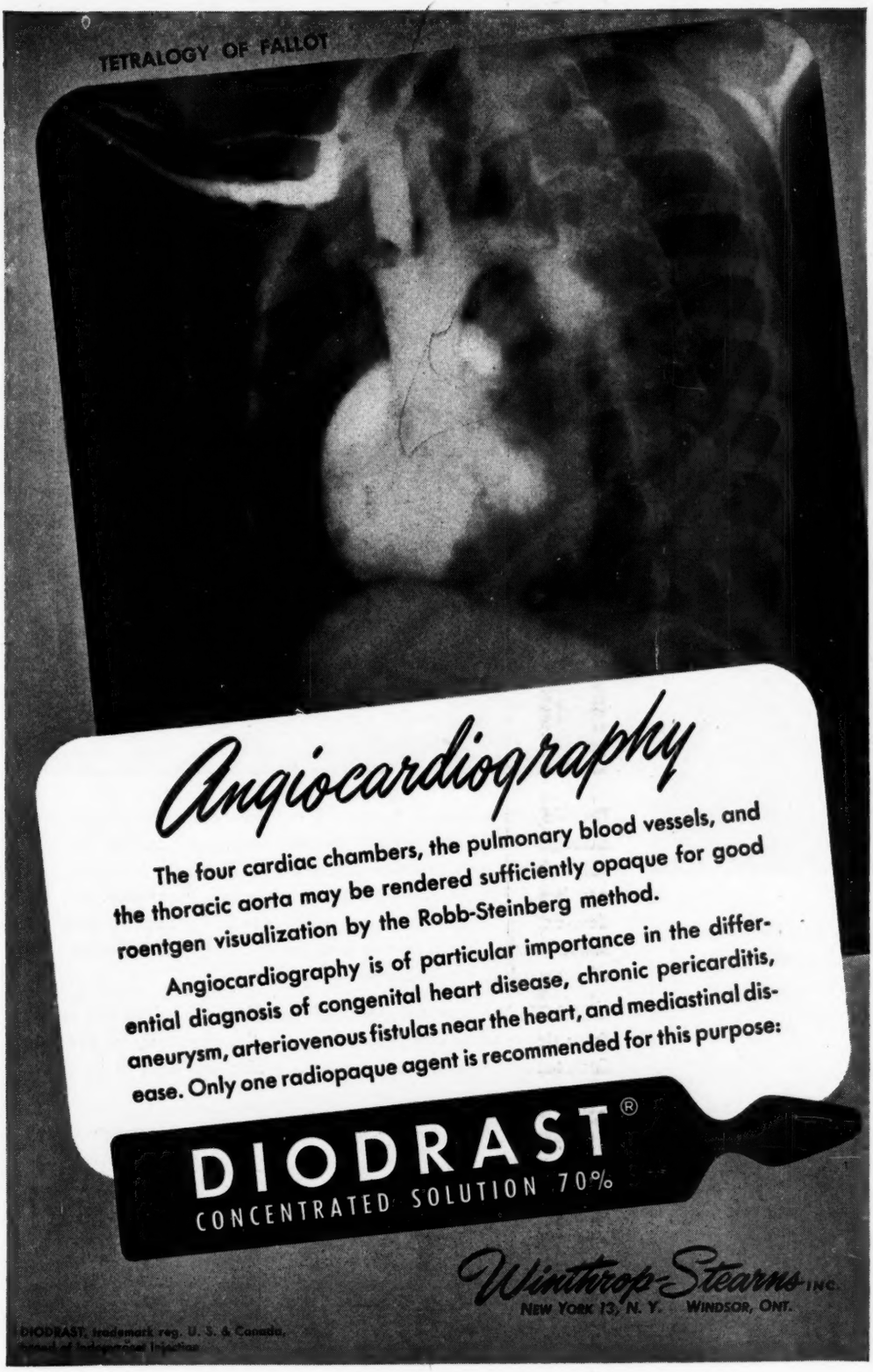

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2. Haid, W. H.: The Use of Screening Tests in the Clinical Laboratory, J. Amer. Med. Tech., *8*:606-14 (Sept.) 1947.

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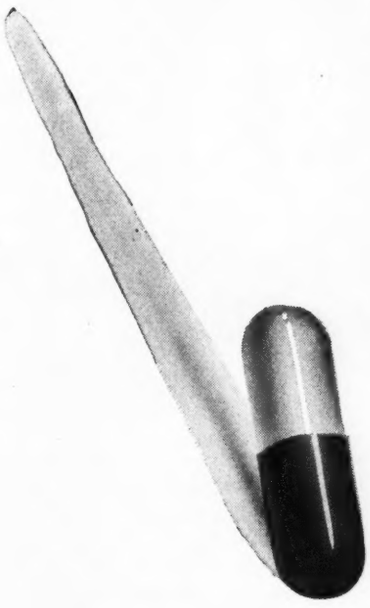

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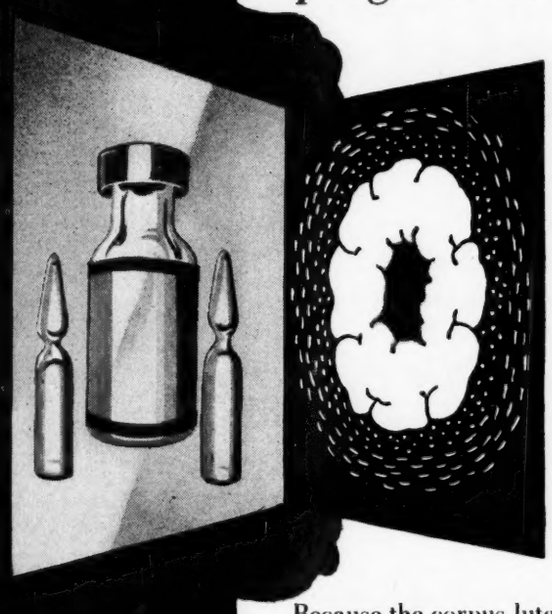

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BIBLIOGRAPHY: (1) Fluhmann, C. F.: J.A.M.A. **135**:557, 1947. (2) Frank, R. T.: M. Clin. North America **25**:607, 1941. (3) Krohn, L., and Harris, J. M.: Am. J. Obst. & Gynec. **41**:95, 1941. (4) Harding, F. E.: Am. J. Obst. & Gynec. **53**:279, 1947.

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The Treatment of Hypertension, editorial, J. A. M. A. 135:576 (Nov. 1) 1947.

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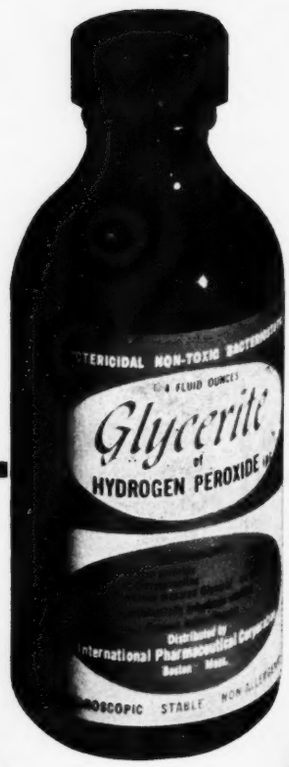

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New Eng. J. Med. 234:468, 1946.
J. Invest. Derm. 8:11, 1947.
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Science 105:312, 1947.
J. Bacteriology Vol. 53, June, 1947.

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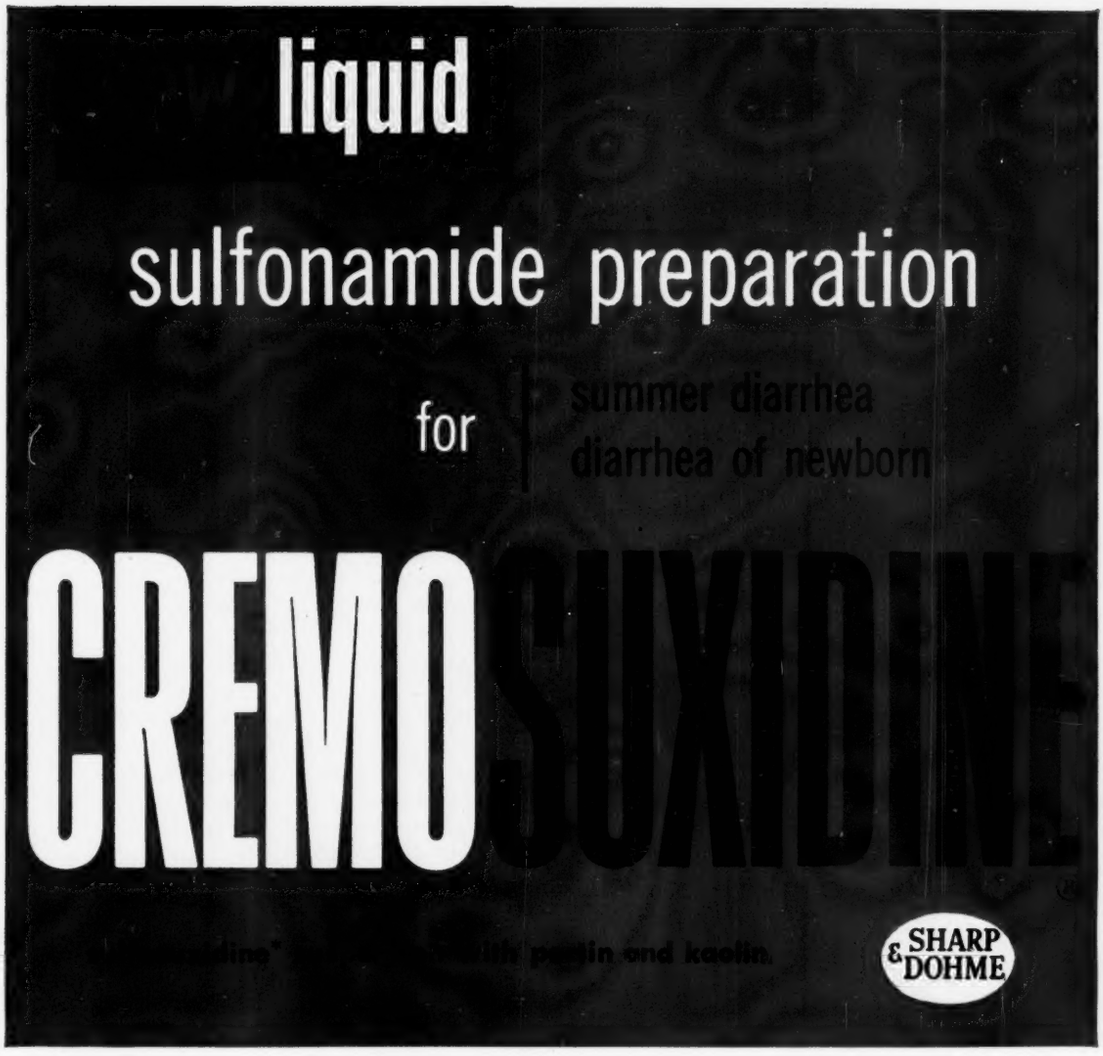

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1. Frant, S., and Abrahamson, H.: *Brennemann's Practice of Pediatrics*, *1*:28:22, 1945.
2. Blattner, R. J.: *J. Pediatrics*, *32*:220, February, 1948.

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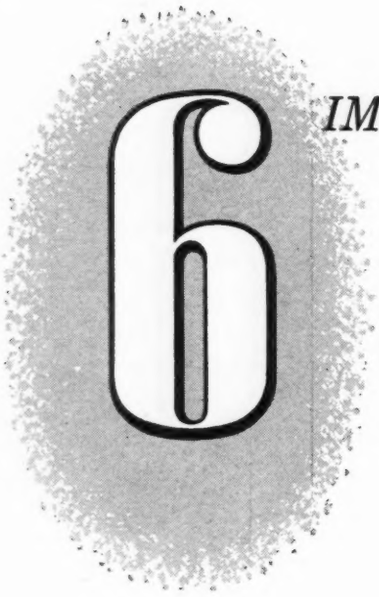

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1. Carroll, G., and Allen, N. H.: J. Urol. 55: 674 (1946).
2. Kirwin, T. J., and Bridges, J. P.: Am. J. Surg. 52: 477 (1941).

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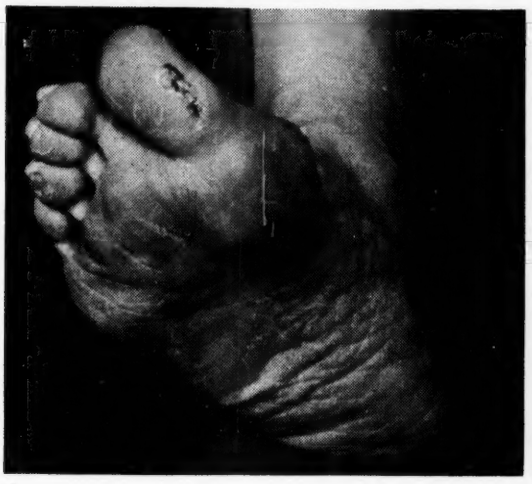

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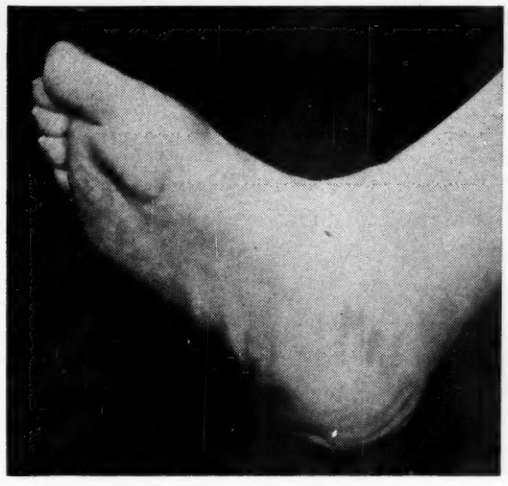

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BOEHME, E. J.	The Treatment of Chronic Leg Ulcers with Special Reference to Chlorophyll	The Lahey Clinic Bulletin, 4: 242, 1946
BOWERS, WARNER F.	Chlorophyll in Wound Healing and Suppurative Disease	Amer. J. Surgery, LXXIII: 37 (1947)
CADY, J. B. and MORGAN, W. S.	The Treatment of Chronic Ulcers with Chlorophyll	Am. J. Surgery LXXV: 4 (1948)
GAHAN, E., KLINE, P.R. and FINKLE, T. H.	Chlorophyll in the Treatment of Ulcers	Arch. Dermat. & Syph. 47: 849 (1943)
HOLMES, G. W. and MUELLER, H. P.	Treatment of Post-Irradiation Erythema with Chlorophyll Ointment	Am. J. Roentgenol. 50: 210 (1943)
LANGLEY, W. D. and MORGAN, W. S.	Chlorophyll in the Treatment of Dermatoses	Penn. Med. Journal Vol. 51; No. 1 (1947)
MORGAN, W. S.	Chlorophyll Therapy A Review of 114 cases	Guthrie Clinic Bulletin, 16: 94 (1947)

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The American Journal of Medicine

VOL. IV MAY, 1948 No. 5

Editorial

Penicillin and Glutamic Acid

More than eight years have passed since penicillin was first used in the treatment of bacterial infections. The chemical structures of several penicillin species have recently been determined, and the drug has even been synthesized in the laboratory. As yet, however, its mode of action is unknown.

Most gram-negative bacteria are able to synthesize the majority, if not all, of the amino acids needed in their cellular metabolism. Many gram-positive organisms, on the other hand, have more exacting nutritional requirements and are unable to synthesize many of the chemical units necessary for protein formation and other metabolic functions. Moreover, the metabolic processes of gram-positive organisms are more susceptible to interference by bacteriostatic agents than are those of most gram-negative bacteria. Recently, E. F. Gale and his collaborators[1–6] have undertaken a systematic study of the metabolism of certain amino acids by both gram-positive and gram-negative bacteria and have investigated the effect of several classes of antimicrobial agents including penicillin upon these important metabolic processes. Utilizing specific decarboxylating enzymes to measure the concentration of selected amino acids within bacterial cells, they have made the following observations relating to the mode of action of penicillin:

1. Gram-positive organisms in general are able to assimilate glutamic acid and lysine from the external medium and to concentrate them within the internal environment whereas gram-negative organisms are unable to do so.

2. Although lysine appears to enter gram-positive cells by diffusion, glutamic acid cannot pass across the cell wall unless energy is supplied by some exergonic metabolism, such as the fermentation of glucose.

3. Once glutamic acid has entered gram-positive micro-organisms, it is present in a free state and serves as a source of amino acid for protein synthesis and other metabolic functions in growing cells.

4. When gram-positive bacteria are grown in penicillin, the assimilatory mechanism for glutamic acid is blocked; and since internal metabolic processes are not affected by the drug, the level of free glutamic acid within the cell decreases to a point where growth can no longer occur.

[1] GALE, E. F. The bacterial amino-acid decarboxylases. *Adv. in Enzymol*, 6: 1–32, 1946.

[2] GALE, E. F. The assimilation of amino-acids by bacteria. 1. The passage of certain amino-acids across the cell wall and their concentration in the internal environment of Streptococcus faecalis. *J. Gen. Microbiol.*, 1: 53, 1947.

[3] TAYLOR, E. S., The assimilation of amino-acids by bacteria. 3. Concentration of free amino-acids in the internal environment of various bacteria and yeasts. *J. Gen. Microbiol.*, 1: 86, 1947.

[4] GALE, E. F. and TAYLOR, E. S. The assimilation of amino-acids by bacteria. 5. The action of penicillin in preventing the assimilation of glutamic acid by Staphylococcus aureus. *J. Gen. Microbiol.*, 1: 314, 1947.

[5] GALE, E. F. Correlation between penicillin resistance and assimilation affinity in Staphylococcus aureus. *Nature*, 160: 407, 1947.

[6] GALE, E. F. and RODWELL, A. W. Amino-acid metabolism of penicillin-resistant staphylococci. *J. Bact.*, 55: 161, 1948.

5. The concentrations of penicillin needed to prevent assimilation of glutamic acid by various gram-positive organisms are of the same order as those needed to prevent their growth.

6. Penicillin-resistant mutants assimilate glutamic acid less efficiently than the sensitive parent strain, there being a quantitative relation between the assimilation affinity and penicillin sensitivity of the organism.

7. Staphylococcus aureus when rendered resistant to high levels of penicillin not only loses its ability to assimilate glutamic acid but also becomes gram-negative and, like other gram-negative organisms, is able to synthesize all of its amino acid requirements from ammonia and glucose in the presence of thiamine.

The above observations from Gale's laboratory strongly suggest that the mode of action of penicillin involves a disturbance in the uptake of amino acids by susceptible bacterial cells. The exact manner in which the penicillin interferes with the assimilation of amino acids is at present unknown.

W. Barry Wood, Jr., M.D.

Symposium on Aviation Medicine

Physiologic Problems in Aviation

HERMAN S. WIGODSKY, M.D.* *and* JAN H. TILLISCH, M.D.†
Washignton, D. C. *Rochester, Minnesota*

THERE are certain physiologic problems that are unique to aviation. Among these problems are those which arise as a result of low barometric pressure—anoxia and decompression sickness. Other problems are those due to cold and to movement—airsickness, acceleration and deceleration.

The physiologist in aviation, through investigation of these problems, is able to provide the physician with a better understanding of the physiologic mechanisms involved, in this way establishing a more rational basis for the diagnosis and treatment of injuries and diseases found in flying personnel. Furthermore, he provides airmen with information concerning the physiologic hazards which face them, permitting them to meet these hazards intelligently. In addition the physiologist also provides engineers with physiologic data necessary for the proper construction of equipment required to neutralize these hazards.

The following is a discussion of some of the more important physiologic problems in aviation:

ANOXIA

The anoxia encountered in aviation does not differ qualitatively from that experienced by mountain climbers. It results from the lowered partial pressure of oxygen in the inspired air. This in turn results from the lowered barometric pressure. Thus at approximately 18,000 feet (5.5 kilometers) the barometric pressure is only one-half of that present at sea level and the partial pressure of oxygen is reduced from the sea level normal value of approximately 160 mm. of mercury to 80 mm. of mercury. At this altitude the hemoglobin of arterial blood is approximately 70 per cent saturated with oxygen in contrast to the normal of 97 per cent. Since the earliest balloon flights of Tissandier, the signs and symptoms of anoxia have been encountered and described. The serious symptoms of acute anoxia encountered in ascent vary somewhat in different individuals. In general, however, as high as 14,000 or 15,000 feet (4.3 or 4.6 kilometers) if exposure is not too prolonged there are few symptoms of anoxia because the compensatory mechanisms provide adequate defense for the body. Above 15,000 feet (4.6 kilometers) the compensatory mechanisms no longer suffice and symptoms of anoxia develop. The most striking of these symptoms are retardation of mental and physical processes, impairment of the special senses, especially vision, pronounced fatigue and frequently changes in personality such as euphoria. From 20,000 to 23,000 feet (6.1 to 7.0 kilometers) unconsciousness usually occurs. The unconsciousness may be the result of failure of either the circulatory or the central nervous system. The after-effects of anoxia are headache, lethargy, nausea and vomiting or severe prostration. Recovery usually takes place in twenty-four to forty-eight hours. In modern aircraft anoxia at high altitudes is prevented by the use of oxygen or pressurization of the air-

* Former Director of Research, Army Air Force School of Aviation Medicine, Randolph Field, Texas.
† Former Chief of Medicine, Army Air Force School of Aviation Medicine, Randolph Field, Texas. At present Consulting Physician, Division of Medicine, Mayo Clinic, Rochester, Minnesota.

craft cabin. A number of deaths have been encountered in military aviation either from improper use of oxygen equipment or in a few cases from failure of the equipment.

EXPANSION OF GASES

The mechanical effects of low barometric pressure encountered at high altitudes result from changes in the volume of gases within the body cavities. Boyle's law states that a given quantity of gas varies in volume inversely in proportion to the absolute pressure exerted on it. The structures most commonly affected by the expansion of gases at high altitudes are the middle ear, the paranasal sinuses and the gastrointestinal tract. Of these the ear is most commonly affected. As the barometric pressure is reduced during ascent, the expanding air in the middle ear causes a pressure sensation and eventually becomes sufficiently great to force the air out through the eustachian tube. The pressure within the middle ear then becomes equalized with the outside pressure. During descent in an aircraft the barometric pressure increases and the pressure in the middle ear falls below that of the external air. With this negative pressure in the middle ear it is difficult, or may be impossible, to open up the eustachian tube. Aero-otitis media is the term used to describe the traumatic inflammation caused by the difference of pressure between the external air and the air in the middle ear.

A phenomenon similar to that which occurs in the middle ear takes place in the paranasal sinuses with changes in barometric pressure. If the sinuses are normal, air passes into and out of the cavities and thus produces equalization of pressure at the usual rates of ascent and descent. If the sinusal openings are obstructed for any reason, as in sinusitis, such equalization of pressure does not take place. The difference of pressure between the air in the sinuses and the external atmosphere produces pronounced pain which may occur either on ascent or on descent.

The gastrointestinal tract normally contains gas which varies in amount. The sources of gas in either normal or abnormal amounts are swallowed air, digestion, fermentation and bacterial decomposition of food, faulty absorption of gas from the gastrointestinal tract and secretion of gas from the blood. Most of the gas is contained in the stomach and the large intestine. During ascent the gases in the gastrointestinal tract expand. Ordinarily, relief is obtained by belching and the passing of flatus. In some persons, however, expansion of gas causes extreme discomfort because of inadequate elimination, pocketing with entrapment of gas in the gastrointestinal tract or excessive gas due to a diet high in gas-forming foods.

DECOMPRESSION SICKNESS

Exposure to low atmospheric pressure such as is encountered at high altitudes may cause another phenomenon in the body, that is, the formation of bubbles in the tissues, blood and other body fluids. This rarely occurs below 25,000 feet (7.6 kilometers). The mechanism is similar to the evolution of bubbles in charged water when the cap of the bottle is removed. The body fluids contain gases, chiefly nitrogen. When the atmospheric pressure is reduced, as in high altitudes, the body fluids become supersaturated with nitrogen and bubbles of gas are formed. The process of production of bubbles, which produces a condition known as "aero-embolism," is the same as the process in caisson disease. It may affect the individual in various ways. The condition known as "bends" is the most common manifestation. The symptoms are pains in the joints, bones or muscles of the extremities. The pain is deep and poorly localized and produces a constitutional reaction out of proportion to its severity. It is aggravated or precipitated by exercise of the affected part. There may be pallor, sweating, faintness, nausea, vomiting or even unconsciousness.

The condition known as "chokes" represents another symptom complex. There is burning substernal distress which frequently is associated with a non-productive cough.

The burning and cough are aggravated by deep breathing and, as a result, the depth of breathing is restricted. The onset of chokes is usually rapid and the symptoms are almost always progressive. The symptoms are ameliorated by descent but residual symptoms may persist after the person has returned to the ground. The exact cause of chokes is not known at the present time but the most widely accepted hypothesis is that the condition is due to pulmonary aero-embolism.

Cutaneous disturbances due to aero-embolism may occur. These disturbances consist in paresthesias and cutaneous rashes. The latter may appear as simple erythema, subcutaneous swelling or ecchymotic discoloration. Defects in the visual fields are encountered infrequently as a result of aero-embolism. Such defects usually are followed by a migraine-like headache. Both the cutaneous and visual disturbances are probably due to embolic phenomena.

Circulatory reactions due to aero-embolism are the most serious complications. These may be divided into two categories: The first is a syncopal reaction, recovery from which is usually prompt during and following descent to ground level. The second type is rare and is much more serious. It is manifested by symptoms of secondary shock at altitude or after descent to ground level following high altitude flight. The type which develops after reaching ground level may be delayed many hours in its onset. The neurologic symptoms which fairly frequently accompany this type of reaction are usually transitory and vary from hemiplegias to paresthesias. The treatment is identical with that of secondary shock resulting from any other cause; however, these patients must be watched carefully for the development of pulmonary edema.

It is appropriate to mention in this section the problem of "explosive decompression"—a term applied to the sudden lowering of pressure within a pressure cabin airplane. Such an event may result from damage to the cabin by enemy action, from failure of the pressurizing machinery to function adequately or from failure of a part of the cabin structure itself. This problem is linked intimately with that of decompression sickness and has assumed a place of major importance with the advent and general utilization of pressure cabin aircraft. The problem of explosive decompression is divided into two parts: (1) the immediate effects due to rapid change of pressure *per se* and (2) the effects due to altitude—anoxia, decompression sickness and cold. The latter effects differ in no way from exposure to high altitude under other circumstances except for the rapidity with which the person is exposed. The immediate effect, on the other hand, poses new problems in regard to the possible injury to gas-containing organs as a result of high pressure differentials developed during rapid decompression. The lungs are particularly important in this regard.

COLD

The problem of cold in aviation differs only slightly from the same problem in any cold environment. However, in contrast with the latter the aviator is relatively restricted in his movements; he encounters cold suddenly (frequently going from tropical conditions to extremely low temperatures in a few minutes) and the cold is frequently accompanied by violent wind blast. The temperatures encountered may be below −60°C. The problem is complicated by the fact that exposure to cold is intermittent and of relatively short duration thus precluding any great degree of adaptation or acclimatization. Exposure to these extremely low temperatures results in frostbite. There has been renewed interest in this physiologic problem in an attempt to establish more reasonable methods of treatment based on the physiologic changes which occur.

ACCELERATION

The problem of acceleration in aviation has increased in direct proportion to the increased speed of aircraft and the im-

provements in structural design enabling aircraft to withstand larger stresses. World War II intensified both the study of the effect of acceleration on the individual and the development of measures and equipment to combat these effects. These studies have been parallel in their growth and have led to a logical development of protective equipment. Until jet and rocket propelled aircraft were employed, acceleration was principally a problem which resulted from aircraft maneuvers such as spins, turns and pull-ups. However, these newer developments pose serious acceleration problems because of very high speed take-offs and variation in take-off altitudes.

DECELERATION

Large decelerative forces are encountered frequently in aviation and are a formidable cause of death. Such forces are met with in crash landings, ditchings, high speed bail-outs and bail-outs at high altitudes when the airman opens his parachute immediately after leaving his airplane. Not only is the problem of deceleration of importance to the engineer, who must construct equipment so that the ability of the human body to withstand these forces will not be exceeded, but it is also of importance to the surgeon who must diagnose and treat the injuries which result from these forces. Diagnosis and treatment will be facilitated if the mechanism of the injury is understood.

Studies to ascertain the limits of tolerance of the human body have been undertaken, using animal and human subjects. It has been possible to reproduce in animals the lesions which occur in human beings subjected to decelerative forces.

Medicine in Aviation

JAN H. TILLISCH, M.D.* *and* FREDERICK R. GUILFORD, M.D.†

Rochester, Minnesota *Galveston, Texas*

MEDICINE in aviation may be applied to two groups: the air crew and the passenger. Factors which may be of great importance in air crew members may have no significance in passengers. As has been mentioned in a previous article, on ascending to altitude certain physical changes which affect the body physiology occur, namely, lowered barometric pressure with resultant decreased oxygen tension and expansion of body gases, changes due to motion, such as acceleration and deceleration, and cold. A further change is the individual emotional response to transportation by air. Because of these changes, it is important to consider carefully two groups of aviation subjects, namely, the air crew and the ill patient to be transported by air. The matter of transportation of the ill patient has been emphasized by Grant,[1] Hippke[2] and Tillisch and his co-workers.[3] The indications and contraindications for the aerial transportation of ill patients are not necessarily applicable to the casual air passenger.

The determination of the status of the cardiovascular system is of importance for both pilot and passenger. A hypersensitive carotid reflex has been shown by Tillisch and Lovelace[4] to be of great importance in the pilot for the reason that it may cause sudden unconsciousness. Therefore a pilot with this condition should be disqualified. The presence of postural hypotension in a pilot is disqualifying for a similar reason as pointed out by MacFarland and his coworkers.[5] At present the most commonly accepted method of examining for postural hypotension is to have the examinee rest in a supine position until a basal blood pressure and pulse rate are obtained. The examinee then stands erect for three minutes and the blood pressure and pulse rate are again taken. If a significant fall in blood pressure and rise in pulse rate occur or if the examinee evinces any signs of unconsciousness, a diagnosis of postural hypotension is made. Evidence of signs of unconsciousness is of more importance than the finding of a fall in blood pressure alone. In the examination for postural hypotension it is also helpful to elicit any history of unconsciousness occurring on rising from a supine position. In passengers neither a hypersensitive carotid sinus reflex nor a postural hypotension contraindicates flying.

Valvular heart disease or hypertension has always been considered a contraindication for flying a plane. This question has not been finally settled. Although there has never been a satisfactory statistical analysis to determine the incidence of sudden unconsciousness in patients who have valvular heart disease or hypertension, it is suspected that it would be very little higher in these patients than in a control group. Yet the chief reason for considering these two conditions contraindications for piloting a plane is the supposed increased likelihood of sudden unconsciousness or weakness. A person with severe hypertension or severe valvular heart disease should not fly a plane. In addition a person with cardiac decompensation caused by either of these two conditions or by any other condition had best fly as a passenger only when absolutely necessary and when there is adequate oxygen available. A person with cardiac decompensa-

* Former Chief of Medicine, Army Air Force School of Aviation Medicine, Randolph Field, Texas. At present Consulting Physician in Division of Medicine, Mayo Clinic, Rochester, Minnesota.

† Former Chief of Air Evacuation, Army Air Force School of Aviation Medicine, Randolph Field, Texas.

tion already has anoxia and the added load of the anoxia of altitude on an already impaired circulatory system may have harmful effects. The nervous tension associated with flying may further aggravate the cardiac condition. In the final analysis a person with mild uncomplicated hypertension or well compensated valvular heart disease can probably pilot a plane with safety. One who has moderately severe hypertension or valvular heart disease with even minimal cardiac decompensation had best not fly a plane. The passenger with either hypertension or valvular heart disease can be transported safely by plane unless he has severe hypertension with a history of the complications of hypertension or unless he has frankly decompensated valvular heart disease; in these latter events the passenger had best not fly. If it is necessary for these patients to fly, oxygen should be administered to them from the ground up.

The rôle of coronary heart disease in aviation has been emphasized by Benson,[6] Graybiel and McFarland[7] and White.[8] This condition is of a more serious nature in the pilot than the aforementioned types of heart disease because of the suddenness and severity of the attacks. Evidence of coronary disease in a pilot should contraindicate flying by that person. Coronary heart disease in the passenger must be handled as an individual problem. It is best not to fly for a considerable period of time after myocardial infarction. A person with easily induced anginal attacks had best not fly. The patient who may have marked apprehension to flying which aggravates his coronary disease had best not fly. A trip by plane that necessitates going to higher than normal altitudes should be contraindicated for a person with coronary disease. Generally the patient who has severe coronary disease should be advised not to fly unless other forms of transportation would put even a greater strain on the heart; if he does fly, oxygen should be administered at any altitude above 7,000 feet and a mild sedative prescribed to allay any nervous tension.

Diseases of the respiratory system vary in their rôle as contraindications to flying. The common cold, sore throat and sinusitis all may increase susceptibility to aero-otitis and aerosinusitis. The application of the usual vasoconstrictor drugs, such as amphetamine (benzedrine) or 2-aminoheptane sulfate (tuamine), may shrink the tissues in the nasopharynx and nasal cavity so that the middle ear or accessory sinuses can be adequately ventilated. Bronchitis, bronchiectasis, pneumoconiosis, pulmonary abscess and bronchogenic carcinoma are not in themselves contraindications to the patient's flying as a passenger unless such conditions are sufficiently severe as to cause respiratory embarrassment. In the latter event these persons should not fly unless oxygen is available and is used. Patients suffering from pneumonia also should be given oxygen when flying even though no evidence of respiratory impairment is present. This is done for the reason that the patient with pneumonia already has endogenous anoxic anoxia and the addition of even a further slight anoxic anoxia as a result of his going to altitude may be sufficient to cause the patient grave trouble. The advisability of flying on the part of a patient with active pulmonary tuberculosis is in question; certainly if the lesion is more than minimal, the patient should not fly. The most important factor in a tuberculous patient's flying is whether or not he has a pneumothorax. The dangers to a patient with pneumothorax in traveling by air are numerous. Rapid contraction and expansion of the collapsed lung are deleterious to the healing process of tuberculosis. Tearing of adhesions attached to diseased pulmonary tissue may result in hemorrhage or in seeding the pneumothorax cavity with tubercle bacilli. Excessive compression of the lung may reduce the vital capacity seriously. Dowd[9] reported the death of a patient with pneumothorax occurring as a result of transportation by plane at an altitude of 16,000 feet.

Persons with asthma should not travel by air during an acute attack and those

suffering from frequent severe attacks should not fly. The person with mild asthma may fly between attacks without difficulty.

Gastrointestinal ailments in crew members vary in importance according to the type of disease. Peptic ulcer, the most common chronic gastrointestinal disease found in pilots, varies in its importance according to the severity of the lesion. A pilot who has an acute peptic ulcer with pain and who is threatened with perforation or hemorrhage should not fly a plane. A pilot who has a healed or a chronic ulcer without symptoms may be able to fly without too great a risk. Certainly a pilot with any evidence of ulcer should be kept under observation for a time to determine the degree of severity of the lesion before being allowed to fly. A passenger with peptic ulcer can be transported with minimal risk except in a case of threatened perforation. In this case if the patient must be transported by plane, he should be flown at a low altitude to obviate the danger of increased intragastric and intraintestinal pressure due to the expansion of gases at increased altitudes. With the use of pressurized cabins in planes this danger will be entirely removed.

Gallbladder disease in a pilot should contraindicate his flying because of the danger that sudden acute colic might render him incapable of flying a plane. Gallbladder disease in a passenger in no way should interfere with plane travel any more than with any other form of travel. The severity of chronic diseases of the small and large intestine in the pilot will determine his ability or inability to fly. In the passenger these diseases are usually of little consequence in determining that person's risk in flying. A disease that is frequently overlooked and yet may be of very serious import in flying is acute gastro-enteritis in the pilot. This disease is of importance in the pilot because of its frequent occurrence and at times its acute debilitating affect which may so weaken the patient that he is incapable of carrying on his duties as a pilot. There have been incidents reported in which a pilot has been suddenly prostrated by acute gastro-enteritis with severe vomiting and diarrhea. The sudden exacerbation of the disease when the pilot is in a plane may be explained by the hyperirritability of the gastrointestinal tract induced by motion of the plane and the expansion of gastrointestinal gases which occurs at altitude. For the passenger this group of diseases is of little significance in so far as the ability to fly is concerned.

Genito-urinary diseases do not play an important part in aviation either from the standpoint of the pilot or the passenger unless they are severe. A renal or ureteral calculus is always a potential danger in a pilot because of the possibility of sudden severe colic and collapse. Gonorrhea in itself is no contraindication to a pilot's flying unless his general physical condition is so seriously impaired that he cannot properly carry out his duties in flying or unless the treatment for the disease might interfere with proper flying.

Active syphilis is adequate cause for suspending a pilot from flying until the clinical signs and symptoms have disappeared and until the patient is non-infectious and has been adequately adjusted to the disease and treatment. With the advances in the treatment of syphilis which have resulted from the use of penicillin and from more rapid treatment with the arsenicals and bismuth, these requirements can usually be met in four to six weeks. It must be emphasized that the serologic test for syphilis is not considered a test of efficiency of treatment or degree of activity of the disease except in early syphilis. Therefore, providing the patient has been adequately treated and there is no evidence of active syphilis, the results of the serologic tests may be ignored in determining the qualification of the person for flying. Syphilis in a passenger does not contraindicate flying unless the disease is in an infectious stage.

Diabetes mellitus of even mild degree occurring in a pilot should be cause for permanent grounding because of the dangers of diabetic coma and hypoglycemic reaction. Observations on passengers with

diabetes mellitus have revealed no serious effects from flying. Hyperinsulinism from any cause is a definite danger when it occurs in a pilot. Hyperthyroidism or hypothyroidism of such a degree as to be clinically evident is a contraindication for a career of flying; either disease in a passenger should in no way interfere with his flying.

Diseases of the skeletal system, such as various types of arthritis, residuals of poliomyelitis and fracture deformities, are to be judged solely by the amount of mechanical interference present in the person handling the controls of a plane.

Aerial transportation of patients who had intracranial injuries was accomplished by the armed services without adverse effect. In order to combat the anoxia of brain tissue associated with increased intracranial pressure, oxygen should be administered from the ground up during flight. Encephalography or ventriculography within the past seven days or any condition in which intracranial entrapment of air is demonstrated is a contraindication to travel by air.

The psychotic patient should not be transported by air because of the difficulty in controlling him on a plane and because of the potential danger that he may get out of control and do damage to the ship and crew. There is no contraindication for the psychoneurotic patient's flying except that these patients are usually more prone than usual to suffer from airsickness.

The patient with severe anemia is already suffering from an anemic anoxia. If that patient is taken to high altitudes, an anoxic anoxia is superimposed and the patient may evince clinical signs of anoxia. Thus the severely anemic patient should receive oxygen on flying to prevent this complication. The slightly anemic patient can usually be transported by air without difficulty because the anemia anoxia is so minor.

SUMMARY

The technical advances in aircraft are lessening the number of medical contraindications for flying. The increased efficiency of oxygen systems and the increasingly extensive use of such systems has made it safer now than formerly for the patient with hypoxia to fly. This includes the patients who have respiratory illnesses, severe or complicated cardiac disease and anemia. The use of pressurized cabins in aircraft will obviate the precautions now necessary in transporting patients who are suffering from conditions that would be made worse by the expansion of intra-abdominal or intrathoracic gas which occurs in unpressurized aircraft. Also, as people become increasingly accustomed to transportation by air and as such transportation becomes increasingly safe, there will be a decrease in apprehension and thus in nervous stimulation, with its side effects, for the individual in flying.

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Neuropsychiatric Problems of the Flyer

R. C. Anderson, M.D.*

Topeka, Kansas

Experience of neuropsychiatrists with flying personnel in World War II has served to establish the fact that the neuropsychiatric problems of such personnel are the same as those which occur in all other environments. The causative agents are the same and the end result is the same. Such a statement may seem superfluous at first glance but it has not always been generally accepted. This is because of the fact that during the development of aviation medicine there was a tendency for medical men to describe entities of disease occurring in flyers largely in environmental terms. This disposition resulted in a fairly widespread belief that many conditions were wholly peculiar to flying personnel. This tendency was probably more marked in the field of neuropsychiatry than in some others. Most of the pioneers of aviation medicine were not primarily interested or qualified in neuropsychiatry. Hence the early flight surgeon was not familiar with neuropsychiatric disorders occurring in any environment. Those that he saw occurring in flyers were described and thought of as distinct and new entities.

This tendency was productive of such terminology as aeroneurosis, aero-asthenia, flying fatigue and so forth. These conditions were described by Armstrong[1] and others quite early. As trained neuropsychiatrists began to take a part in aviation medicine they recognized that all of this terminology was composed of new names for old friends —the various neurotic reactions. This viewpoint was not greeted with enthusiasm or wide acceptance at first by the majority of those interested in either aviation or aviation medicine. The term "neurosis" carried a certain stigma which both the aviator and the doctor were loath to associate with the highly selected individual who was the peacetime flyer.

While World War II afforded an increased opportunity for the consideration of neurotic reactions in flyers, it also afforded a further opportunity to avoid distasteful terminology. The term "war neurosis" came into widespread use and as applied to flying personnel was known as "operational fatigue." This term not only implied a condition peculiar to aviation but also to combat or operational flying. Actually it was no more peculiar to flying than to any other activity accompanied by the same type and amount of stress and it was likewise not peculiar to combat. Grinker and Spiegel[2] have recently stated that war neuroses (including operational fatigue) are in reality psychoneuroses.

The peacetime aviator develops the same type of neurotic disturbances as does the combat flyer and for the same reasons. The incidence is less in the peacetime aviator because the quantity of stress is less and the individual is more highly selected. Too much emphasis should not be placed on this last factor however. Selection as nearly perfect as is possible will not guarantee that the individual will not be subjected to intolerable stresses resulting in a neurosis. Obviously the possibilities for such stress situations are greater in an environment with the admitted and ever present dangers of aviation than in most other peacetime environments.

The causative agent of the neuroses of flyers is anxiety as is true of all other neuroses. The individual method of expression of that anxiety determines the form of reaction presented by the patient. This

* Former Chief of Psychiatry, Army Air Force School of Aviation Medicine, Randolph Field, Texas.

allows for a wide variation of syndromes and symptom complexes. However, allowing reasonable latitudes there are certain general reaction types which occur more frequently than others in flying personnel. One feature which tends to distinguish the neuroses of the flyer from those of the average individual is the strong conscious component which is usually present. Often this conscious element is the presenting one, such as "I'm scared to fly." The doctor not trained in neuropsychiatry is apt to call such a condition simple "fear" and to overlook its true meaning and significance. These facts have been nicely described by Bond.[3]

TYPES OF REACTIONS

Phobias. Of all the neurotic disorders to which flyers are subject by far the most common is phobia. Not only does this phenomenon occur alone but in many instances in which other syndromes predominate phobic manifestations are accompaniments. A phobia is defined as a morbid fear of a specific situation or thing. The student of psychopathology knows, however, that such a symptom may be a clever disguise for the true underlying situation. This is especially important to bear in mind in the phobias of flyers.

The conscious expression and presenting symptom of the flyer's phobia usually takes the form of a fear of flying a particular type of aircraft, or more rarely all aircraft, a fear of a particular type of flying such as night flying and fear of flying over certain types of terrain. Superficially it seems that an isolated activity has been made the focus of conscious anxiety. This is true but what is equally true, and often overlooked, is that the same activity is the focus of a great deal of anxiety concerning the origin of which the individual is unconscious.

Such a patient is usually able to regard his symptoms objectively. However, he finds that the amount of anxiety which is attached to the specific focus is out of all proportion to his conscious desires and beyond his conscious understanding. The patient can give no reason why flying which was formerly a pleasure has now become a source of unreasoning fear. The conscious expressions of fear which such a patient offers are in reality just as much "conversions" as are the more dramatic symptoms of hysteria. The only difference is that the symptom is expressed mentally instead of physically.

Very often the fatalistic attitude which most experienced flyers adopt sooner or later resolves itself in the conviction that death in an airplane is inevitable. If the flyer is subjected to a series of minor escapes from death or considerable time elapses, this conviction may be unconsciously expanded to include the premise that each flight will be the last. Often identification with a dead friend who was "a better pilot than I" may strengthen this conviction. The flyer takes off on every flight unconsciously saying to himself in the best Hollywood fashion, "This is it."

As such a situation as that described continues, the flyer builds up an enormous amount of anxiety about the true origin of which he is unaware. The fact that something does not happen to him becomes more disturbing in effect than if something did. The next step is the displacement of this anxiety to some isolated activity and thus the phobia results. The mechanism of displacement is frequently utilized by the neurotic flyer and it, together with identification, accounts for most of his difficulties.

Perhaps more rarely the true origin of the phobia may lie in the flyer's interpersonal relations. Thus he develops an aversion to a particular type of plane in order that he may be moved from an organization in which there is some individual particularly distasteful to him. The underlying emotion of hate is not consciously experienced in such an instance any more than is the true fear from which the individual in the first group suffers.

That a large part of the phobia is unconsciously motivated is attested by the tendency for such reactions to "spread." Once the pilot has a definite phobia for a particular type of aircraft his symptoms are usually

not long alleviated by being removed from that aircraft. The phobia encompasses succeeding types of airplanes, succeeding types of flying and so forth, and becomes more and more crippling as time progresses. Because of these characteristics the prognosis is relatively bad in such a reaction.

The phobias are usually stubborn and resistant to treatment. The underlying emotions are firmly repressed and it is difficult to bring them to light and develop true insight. If the patient attempts to carry on as a flyer in the face of his phobia, he may have psychosomatic symptoms as secondary expressions of his repressed emotions. "Tension headaches," vertigo and so forth are the most common of these. Such patients are prone to carry on as long as possible since they suffer from the same fallacy of conscious reasoning that the observer may, and do not wish to admit "cowardice." Such a patient may be quite comfortable and symptom-free if not exposed to the precipitating stimulus. This is characteristic of all phobias. Thus the flyer may have no further difficulty if he renounces flying but obviously this does not constitute a cure.

Anxiety Reaction. Although phobia formation constitutes one of the most frequent neurotic symptoms of the flyer, the syndrome designated "anxiety state" or "anxiety reaction" is the most common generalized manifestation. Various phobias may form a part of this picture but in the anxiety reaction the disturbance of the personality is more widespread than in simple phobia formation.

It is the anxiety reaction which formed the major part of conditions known as "operational fatigue" in combat flyers. However, it can and does occur in non-combat flyers. Classically, it may be the result either of long-continued minor stress or a single overwhelming experience. The opportunities for the latter are somewhat greater in combat, but it is important to bear in mind that the peacetime aviator is subjected to long-continued minor stress.

Characteristically, this reaction takes place in a series of steps denoting its increasing severity of manifestation. The first of these steps is usually disturbances of sleep. In the beginning this takes the form of difficulty in going to sleep. The patient who has been able to dissipate a portion of his anxiety and tension in activity during the day is unable to do so in the quiet immobility and darkness after going to bed. Consequently his anxieties seem intensified at this time and he is unable to relax and go to sleep. When sleep is finally attained, the next disturbance is in the form of dreams. These are occupational in nature and usually involve the patient in frightening accidents and emergencies. He dreams of crashes, of stalling out and catching on fire. Also common is dreaming of unsuccessful attempts to land the airplane. These dreams are often accompanied by talking and even walking in sleep and also may awaken the patient. All of these phenomena interfere with rest as they persist and increase so that the patient has the burden of physical fatigue added to his other difficulties.

The next step in the development of the anxiety reaction is the appearance of states of partial dissociation of consciousness in the daytime. Partially as a result of his disturbed rest the patient is apt to be subject to drowsiness in the daytime. In severe cases this may produce the "startle reaction" to sudden stimuli. Also, as the anxiety increases the patient logically becomes introspective and preoccupied with his thoughts and his problems which results in a partial detachment from his surroundings.

The next step is the appearance of a personality change. This is due to the patient's realization that something is wrong and his inability satisfactorily to explain it as the result of his introspection. The personality change follows no set pattern but usually takes the form of expression of characteristics which are opposite to the patient's usual personality. Prominently associated with this is depression of mood, which may be severe in degree, and extreme irritability. The latter may be the most prominent feature to the casual observer.

The patient is also self-conscious and may develop mild ideas of reference, believing that others are "watching" him, and so forth.

Accompanying all this are the usual somatic concomitants of anxiety. The patient experiences palpitation of the heart, dyspnea and urinary frequency. Loss of appetite is common and contributes to loss of weight. Objectively the patient shows coarse tremors. The use of tobacco and alcohol may become excessive.

The success of treatment of this condition varies with the stage in which it is recognized. In common with all neurotic disorders the earlier treatment is begun the better is the prognosis. If the condition is recognized in the earlier stages of disturbances of sleep and fatigue, excellent results may be obtained by temporary respite from flying duties, sedation and simple explanation and reassurance. Beyond this stage psychotherapy must be much more intensive and results are not nearly so encouraging. The most common mistake which is made is to expect that grounding the patient will relieve the symptoms of a fully developed and long-established neurosis. Simply removing the stimulus does not alter such behavior patterns once they are firmly established and this fact has been a source of disappointment and misunderstanding to the patient and physician alike. Rest alone does not cure neuroses.

Reactive Depression. As indicated in the preceding section reactive depression may be a symptom of some of the other types of disturbance. However, more rarely this may be the predominant reaction. The depth of depression may be great and it may be difficult to distinguish from a true depression.

The more severe forms of reactive depression in flying personnel are usually the result of identification with dead friends or the assumption of responsibility for the death of others in crashes and collisions. Very often the true underlying cause may be repressed hostility toward those who are dead. In the opinion of this writer, however, such ambivalence is not necessarily present and straight identification can occur without it.

The individual who has identified himself with a dead friend or associate may arrive at the same conclusions regarding the inevitability of death in an airplane as was described in the discussion of phobias. Instead of a phobia a profound depression may develop as the result chiefly of his own personal characteristics. Those who develop depressions in such circumstances are usually somewhat immature and narcissistic in their personality make-ups. I have seen several such patients in whom a lifelong phobia of death itself was accompanied by childish fantasies of never growing old or never getting sick.

The patient with a moderate reactive depression is frequently overlooked by his lay associates and sometimes by the physician. This is especially dangerous because the retarded psychomotor processes of such an individual may constitute a real menace to the safety of himself and others if he continues to operate an airplane. Careful investigation should be made of those flyers who are often described as having lost interest or being difficult to deal with. Patients with severe cases are usually recognized easily. The patient shows a facies of hopelessness, retardation of thought and activity and has loss of appetite, sleeplessness and so forth. Overlooking a patient with reactive depression or forcing the aviator so affected to fly may result in suicide. The airplane is a convenient instrument of self-destruction which may explain some "unexplained" crashes.

Fortunately this group of patients probably responds better to treatment than any of the others if that treatment is prompt and intelligent. It goes without saying that the patient must be temporarily suspended from flying duties. He then must be given insight into his identifications, and the lack of logic for his assumption of responsibility for matters entirely beyond his control must be pointed out. This type of patient is always wholly unconscious of these matters. If the

patient is intelligent and the therapist is skillful, the response to this type of management is dramatic. The patient may show an almost complete reversal of attitude in a short time.

Neurasthenic Syndrome. Prominent among the neurotic disturbances of flyers is the neurasthenic syndrome. This is the result of displacement of anxiety arising from other sources to the focus of physical symptoms. The neurasthenic flyer does not differ clinically from his counterpart in any other activity but, as has been pointed out, the environment of flying itself may provide him with some anxiety which he may choose to handle in this manner. The neurasthenic type of reaction tends to be insidious in onset and consequently is not usually seen as the result of one or two severe traumatic experiences. Rather, it develops gradually as the result of minor and long-continued stress. It is important to bear in mind that the responsible factors may be wholly unrelated to flying.

The neurasthenic syndrome is usually the response of individuals who are unhappy and dissatisfied with their environment in general. Many flyers learn that their profession is not all glamour but are either unprepared for other activities or unwilling to admit failure. They may express the anxiety arising from this situation as anxiety concerning their physical health. Their symptoms are of the hypochondriacal type familiar to every physician.

The symptoms of the neurasthenic flyer in themselves do not prevent him from flying. Usually he expresses himself as believing that he should not fly until they have been alleviated, or that he cannot be expected to fly efficiently feeling as he does. No anxiety is ever expressed directly related to flying. The patient is perfectly willing to fly and desires to fly even if he is told that this is inadvisable. The only concern which the patient expresses is in regard to his health and he is persistent in his efforts to improve it. Often in flyers the symptoms may take the form of exaggerating physical defects. Thus the mild sinusitis becomes worse, there is increasing difficulty in clearing the ears and so on.

All neurasthenic patients are relatively recalcitrant to treatment and flying personnel is no exception. The reaction is usually related to deeply-seated personality traits which are difficult to modify. Successful treatment of any neurasthenic usually involves an extensive alteration of the patient's environment. If the flyer's difficulties do not stem from flying itself, this may be accomplished. If the patient's basic difficulty is flying, he cannot be successfully treated as a flyer. Those patients in whom actual organic defects are exaggerated are especially difficult to deal with. A word of caution is in order concerning the symptomatic treatment of the neurasthenic patient. This is frequently done and results in the physician's literally "chasing" the symptoms all over the patient's body. The patient may be expected always to remain one step ahead of the treatment by the mechanism of displacement. Some neurasthenic flyers may continue to function somewhat inefficiently as flyers in peacetime aviation. Obviously this is not desirable from the viewpoint of either the patient or others.

Conversion Phenomena. Hysterical conversion phenomena of the dramatic and obvious type usually described are not too common in flying personnel. It is generally recognized that these phenomena have had a decreasing incidence in general for the past several years. An occasional flyer, particularly the neophyte, may develop the classical paralysis or anesthesia identified with hysteria but this is relatively rare. During the war a few cases of hysterical amblyopia were reported including a case in which a totally "blind" cadet was safely guided to a landing.

It has been established fairly recently, however, that flying personnel do present a fairly large number of conversion phenomena which are much more obscure and can be detected only by painstaking investigation in many instances. These are chiefly related to the special senses and are often of a type which do not totally in-

capacitate the flyer but protect him from special types of flying. From the beginning of aviation sufficient medical emphasis has been placed on the senses of sight and hearing for their importance to be thoroughly appreciated, and perhaps overestimated, by the flyer. Hysterical symptoms referable to these functions therefore are quite logical.

Such symptoms usually take the form of mild impairment of visual acuity, depth perception, night vision or hearing. Diminution of visual acuity is a common response to an aversion for instrument flying. The weakened eyes cannot tolerate the strain of continued observation of instruments. Similarly, disturbances of depth perception are utilized as protection against formation flying and to explain poor landing technics. Defective night vision protects from night flying. Many cases of "aviation deafness" occurring in young flyers with only 300 or 400 hours of flying experience are hysterical in origin. Often they do not bother the individual except with reference to the intercommunication system. Thus he cannot instruct and communicate with his student, he cannot fly multiplaced ships and converse with his crew. Defective hearing is also utilized to protect from instrument flying and in many instances the flyer can hear everything perfectly with the sole exception of the radio "beam." Very few such patients are malingerers as might be expected. The deception of the true malingerer is not readily exposed and is not influenced by suggestion as are the symptoms of these patients. As is characteristic in all cases of hysteria the patient accepts his disability philosophically and is anxious to carry on as best he can in the presence of the impairment.

Symptoms of this type are amenable to treatment as far as their removal or improvement is concerned and respond readily to simple suggestion and reassurance. However, this in no way guarantees against their recurrence or the substitution of new symptoms. Consequently, for the flyer who has this type of reaction the prognosis for future usefulness in flying is guarded. In peacetime aviation it may be possible to assure that such a flyer need not participate in those types of aviation distasteful to him.

Psychosomatic Disturbances. This is a group of conditions often confused with conversion phenomena. In these conditions, however, the symptoms do not represent the conversion of anxiety into the physical symptoms of hysteria. Instead, they represent the individual's expression of anxiety through lower visceral centers. One of the best descriptions of this group of disturbances has been given by Grinker and Spiegel.[2]

Recognition of psychosomatic diseases has increased greatly as a result of the war just concluded. By and large they formed the largest problem with which the military physician had to deal. The visceral system most often disturbed was the gastrointestinal system and if one considers the early steps of personality development the use of this system by the patient to express emotion becomes quite logical. Most of the "dyspepsias," "ulcer syndromes" and so forth seen in American troops had their origin here. This fact was also recognized by our enemies although their understanding of the etiology may have been imperfect. The surgeon of the German Luftwaffe is quoted as having said, "The psychological diseases of World War I become physiological diseases in World War II. The soldier who had an hysterical paralysis in World War I, vomited in World War II."[4]

With reference to the flyer this group of disorders is probably of most significance in relation to so-called airsickness. It is not meant to imply that airsickness, or preferably motion sickness, does not exist on an etiologic basis which is chiefly physiologic. A few simple experiments with exposure to the effects of motion will convince the most confirmed skeptic of that. In common with most disturbances of the human organism, however, this is one in which it is most often impossible to draw a hard and fast line between the psychic and somatic factors responsible. About the most that can be hoped for is to determine which factor seems to predominate in the given case. There are

many cases of airsickness in which the psychic factor predominates to the extent that the physical one is of negligible importance.

In many cases of airsickness it can be readily demonstrated that there is little or no relationship between the symptoms and motion or other purely physical factors. This includes those patients in whom vomiting is precipitated by the sight of an airplane or begins before the plane is air-borne. The fact that some of these patients respond to various motion sickness preventatives does not alter the basic premise. Most of these remedies are composed of sedative drugs in various combinations. Many experienced flyers who are ordinarily not susceptible to motion sickness recognize the fact that they are more apt to be susceptible if they are "nervous" or worried about something. Some cases of airsickness may represent conversion phenomena but ordinarily the hysterical patient does not choose symptoms so disagreeable and prostrating as these. Occasionally the flyer may be subject to diarrhea just prior to flights or after their conclusion. This is another way in which the gastrointestinal tract "speaks." The writer has seen one high-ranking flyer officer of long experience in whom this was a regular phenomenon.

The treatment of these disturbances follows that of all other psychosomatic complaints. Most important is the recognition of the true underlying etiology. Intelligent patients under skillful therapists make excellent recoveries in many instances following the development of insight. As in all other forms of psychotherapy much depends upon the therapist, the transference he can establish and the reassurance he can give. In military aviation the time involved in dealing with such patients is usually not available as a routine procedure. In the case of the peacetime flyer and in key personnel it might be.

SUMMARY

The foregoing constitutes a general description of the psychiatric ills to which the flyer is heir. It is easy to recognize the fact that leaving the earth for the alien environment of the atmosphere produces no new syndromes. The individual personality continues to react with its environment in much the same ways regardless of what the environment may be. Some environments may contain more situations of stress and hence be productive of a relatively higher incidence of neurotic reactions than are others. The individual's response to stress tends to be the same regardless of where he may be. Since this is true it goes without saying that the neuropsychiatric problems of the peacetime aviator are qualitatively the same as those of the combat flyer. Quantitatively there may be some difference.

The most important point to bear in mind is that the best treatment of these reactions is prophylaxis. In war this is vastly more difficult than in peace. All flyers should be assured of adequate rest and relief from flying duties so that they do not become "stale." Adequate recreational outlets for the increased tension borne in the air must be provided and encouraged. Early symptoms of impending neurotic disorders and psychosomatic disturbances must be promptly recognized, their basic origin determined and appropriate psychotherapy begun before irreversible behavior patterns are established. The physician must be aware of the potentialities present and not be content to give the patient ever changing symptomatic treatment. In short, the intelligent management of the neurotic flyer is the same as the intelligent management of all other neurotics. It follows that the procedures of mental hygiene are also the same.

A final word of warning is in order concerning an old fallacy that all neurotic disorders might be prevented in flyers and others by proper selection of personnel. The experience of the war has shown this not to be true. This is because even the most stable and well adjusted personalities do not represent perfection. Consequently there is always a weak spot in the personality armor which may succumb only to a specific stress to which it is sensitive. It is

impossible to predict whether or not the individual will be exposed to the specific stress he cannot tolerate. In some of course the weak spot is large. In others it is small. So-called predisposition is important, therefore, in a quantitative sense but to a considerable degree all individuals are predisposed.

Another fallacy exploded by the war is that the known neurotic cannot fly successfully. Hastings, Wright and Glueck's[5] report of 150 successful combat pilots, 50 per cent of whom had histories of pre-existing instabilities sufficient to be considered evidence of neuroticism by most standards, serves to emphasize this point. In many cases flying itself may afford the individual relief from his basic conflicts and an outlet for his basic anxieties. This is not meant to imply that neuroticism is a favorable characteristic. All things being equal the efficiency of the non-neurotic is likely to be greater than is that of the man who starts any activity with a neurosis already established.

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Use of Drugs at High Altitude

PAUL K. SMITH, PH.D.*
Washington, D.C.

IT is important to determine if drugs frequently employed in aviation medicine act differently at high altitudes. Modification of action under such conditions might occur because of diminished barometric pressure, partial anoxia or extreme cold. Various attempts have been made to use drugs to improve altitude tolerance and to relieve the pain of decompression sickness. Evidence is lacking that many substances actually increase altitude tolerance. It is unlikely that any drug will be more than moderately effective so far as intensity or duration of action is concerned. During the war emphasis was placed, almost certainly correctly, on improvements in oxygen equipment rather than on temporary and uncertain measures designed to enable men to get along with unsatisfactory equipment.

Various dietary factors have been given considerable attention in the belief that such measures would be more lasting and physiologic. It is suggested from studies of visual[1] and psychomotor[2] performance that the ingestion of large amounts of glucose will improve performance under hypoxic conditions. There is some evidence that a low blood sugar interferes with oxygenation of the central nervous system[3,4] so that a simultaneous mild hypoxia and hypoglycemia produce symptoms similar to those associated with severe oxygen lack and normal blood sugar. This may be justification for supplying foods rich in carbohydrate to personnel immediately before they fly to high altitudes.[5] Experimentally 50 Gm. or more of glucose has been employed with moderate improvement in performance.[1]

Some time ago it was reported that animals on a carrot diet were more resistant to the lethal effects of hypoxia than animals on an ordinary diet.[6,7] This has been confirmed[8] but when a loss of reflex response or electroencephalograms were used as criteria[9] no improvement was noted. So far no dietary factor other than glucose has been demonstrated to be of definite value.

Experimentally, subconvulsive doses of apomorphine, camphor, tetrazol, potassium cyanide and strychnine have all been shown to protect against the lethal effects of anoxia in mice but the respiratory stimulating effect may have been the most important factor.[10] Under similar conditions full narcotic doses of ethyl alcohol are effective, perhaps through a general reduction in metabolism with a subsequent diminution in oxygen requirement.[11] Anesthetic doses of amytal or of pentobarbital sodium were not beneficial but moderate doses[12] of diphenylhydantoin sodium gave some protection. Further studies of agents affecting the autonomic nervous system[13] revealed that cholinergic and sympathicolytic drugs protected against the lethal effects of acute anoxia in mice but adrenergic agents increased the lethal effects. In general, drugs which increase the metabolic rate, such as thyroxine and dinitrophenol,[14] diminish hypoxia tolerance.

Several studies have shown that the adrenal cortex is involved in some manner with tolerance to oxygen deficiency.[15,16] During the initial phase of anoxia the blood sugar is normal and the amount of glycogen stored in the liver is diminished. This may result from an increased utilization of carbohydrate. Further adaptation to anoxia involves increased protein catabolism with a rise in carbohydrate stores and an increase

* Former Chief of Pharmacology, Army Air Force School of Aviation Medicine, Randolph Field, Texas.

in urinary nitrogen. These changes did not take place in the absence of the adrenal cortex and injections of adrenal cortical extracts[16] greatly increased the survival rate. Desoxycorticosterone acetate and 17-hydroxycorticosterone were ineffective. In spite of the promising experimental evidence of effectiveness there are no clinical data to justify the use of cortical extracts to increase hypoxia tolerance.

Since carbon dioxide is such an effective respiratory stimulant, several attempts have been made[17–19] to utilize it to increase anoxia tolerance. Its effectiveness has not been established with certainty but the ultimate result seems to depend on whether or not the inevitable reduction in alveolar oxygen tension is more than compensated by increased minute respiratory volume, cerebral vasodilatation and shift in the oxyhemoglobin curve.

Under conditions of partial anoxia certain analeptics such as benzedrine, desoxyephedrine (methedrine) and caffeine improve psychomotor performance.[9,20,21] There is some evidence that benzedrine is superior to caffeine for this purpose. Whether or not a mild respiratory stimulating effect of the drugs could be responsible for the result is not known.

DRUGS ALLEGED TO REDUCE HYPOXIA TOLERANCE

It has been important to determine whether or not certain drugs sometimes administered routinely to flying personnel, such as the antimalarial drugs and the sulfonamides, diminish altitude tolerance. This has presented problems of measurement of great complexity since it is insufficient to know merely that such drugs do not of themselves endanger life at high altitudes, but whether they interfere in any way with the most efficient performance of duties. Obviously only study of human subjects is satisfactory and this requires careful evaluation of such factors as adaptation, learning and motivation. These problems have been partially solved by the use of multiple psychomotor tests.[22]

Because of the use of sulfonamides in ambulatory patients, several studies have been made of the effects of these on the performance of certain tasks. If anemia or methemoglobinemia is associated with the administration of a sulfonamide, there is little doubt that hypoxia tolerance is reduced. This rarely occurs, however, except with sulfanilamide and since clinically this drug has been replaced by less toxic ones the danger from such an effect is small. Moderate doses of sulfanilamide affected an adversely psychomotor performance[23] but under similar conditions sulfathiazole and sulfadiazine were without effect. However, some studies of sulfathiazole and sulfadiazine show that visual depth perception and the muscle balance of the eyes is affected[22] although no differences in mental efficiency or hand-eye coordination were observed.[22,24,25] Tests at simulated altitudes[22,26] have failed to show any decrement in psychomotor performance with either sulfadiazine or sulfathiazole.

The antimalarial drugs have been widely employed in suppressive doses and it has been necessary to determine carefully whether or not they interfere with flying efficiency. Many of the toxic effects of quinine, such as visual and auditory disturbances, will obviously interfere as will the irritating effects of quinacrine hydrochloride (atabrine)[27] on the gastrointestinal tract, but more attention has been directed to determining if reduction in oxygen tension will accentuate these effects or introduce new ones. Fortunately quinine, atabrine[27] and chloroquin[28] are not demonstrably more toxic at 18,000 feet simulated altitude than at ground level.

Because of the frequent use of morphine in battle casualties and its known ability to depress respiration, studies have been made to determine if the toxic effects of morphine are enhanced at high altitudes. One early study on mice[29] revealed a marked increase in fatality rate; all animals who received morphine died at 27,500 feet and all controls survived. Other studies on human subjects have revealed no serious

respiratory depression[30,31] although maintenance of blood oxygen varied in different subjects. It was somewhat diminished in those subjects whose reflex excitability was poor.

RELIEF OF DECOMPRESSION PAIN

Little progress has been made in the search for drugs for the relief of decompression pain. Because of its respiratory depressant effects, there is some hesitancy to use morphine but a more serious objection is its relatively slow onset of action[31] in a condition which frequently will lead to serious collapse. Certain, more rapidly acting analgesics are suggested and some preliminary studies in which an ampule of trichlorethylene was crushed in the oxygen inlet showed that it had promise as an analgesic, but it occasionally gave rise to cardiac disturbances and it should be used with caution if at all. A 20 per cent mixture of nitrous oxide is known to be a good analgesic[32] but such a mixture with oxygen may be explosive. The synthetic analgesic, demerol, is almost as slow in its action as morphine after subcutaneous administration.

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Treatment of Airsickness with Drugs

PAUL K. SMITH, PH.D.*
Washington, D.C.

AIRSICKNESS is a form of motion sickness to which most people probably are susceptible depending on the duration of flight, type of plane, position in plane and the weather as well as other undetermined factors. Certain factors, such as apprehension and fear, are believed by some to be more important in airsickness than in other forms of motion sickness. Air passengers in both military and civilian life may have had but little flying experience or may fly so infrequently that adaptation does not occur. It is in this group that drugs may be of greatest value. Studies in the air forces have shown that the incidence diminishes rapidly with experience in the air.[1]

The movement of aircraft is highly erratic and depends on the type of aircraft and the weather conditions to so large an extent that other devices have been used for producing motion sickness. The most widely employed has been the simple swing.[2] Others have included vertical accelerators[3] and rotating chairs.[4]

A drug for the relief of airsickness should prevent airsickness without producing any other pharmacologic effects. It should be active after oral administration and the onset of action should be immediate. It should not be toxic, habit-forming or cause disagreeable symptoms. At present remedies are available which will decrease the incidence of airsickness to about one-third without producing appreciable side effects. In general the drugs used have been those that have been employed in seasickness or drugs related to these. Most of them are either central nervous system depressants such as barbiturates, central nervous system stimulants such as benzedrine or parasympatholytic agents such as drugs of the atropine series. Various criteria have been employed in evaluating the remedies but in general vomiting alone as the chief criterion is usually the most reliable.

It is surprising that many studies have been made on motion sickness with mixtures of drugs without first determining the effectiveness of the component drugs. Frequently the central nervous system stimulants have been incorporated to prevent undue depression and in some as many as seven different drugs have been employed simultaneously.[4]

The most promising group of drugs have been those with parasympatholytic action such as atropine and related drugs. Of those of demonstrated effectiveness, atropine, hyoscyamine and hyoscine (scopolamine) are the most effective. On the basis of their effect on motion sickness alone there is not much difference between these three drugs. However, it has been demonstrated that the suppression of salivation is less with hyoscine than with atropine or hyoscyamine when they are all used in effective doses.[5] For this reason hyoscine has been employed most frequently although there is little evidence that it is actually superior in its ability to relieve motion sickness. It has been shown to be effective in seasickness,[6] swing sickness[7] and airsickness.[8,9] The doses that have been employed most commonly are 1.0 mg. of atropine sulfate or of hyoscyamine hydrobromide or 0.65 to 0.75 mg. of hyoscine hydrobromide. The onset of action after the oral administration of the drug is not very rapid, about one hour being required for an appreciable suppression of salivation. The actual duration of action of these drugs is not known but there

* Former Chief of Pharmacology, Army Air Force School of Aviation Medicine, Randolph Field, Texas.

is some evidence from studies on swing sickness that the effectiveness lasts for approximately six hours.

The central nervous system stimulants that have been employed include ephedrine, benzedrine and methedrine (desoxyephedrine). There is not sufficient evidence to justify the belief that they are effective remedies for motion sickness, either alone or when incorporated with other substances. These drugs are usually used in combination with central nervous system depressants in an attempt to prevent undue depression without detracting from the effects of the drugs on motion sickness.

The barbiturates are of particular interest because many of them had been incorporated in drugs for treatment of motion sickness and have been widely employed without definite knowledge of whether the barbiturates themselves contributed anything to the effectiveness of the remedy. In the opinion of some[10] the action of the barbiturates and thiobarbiturates in motion sickness is not related to the depressant action on the central nervous system. Several barbiturates have been studied including the long-acting ones such as sodium barbital and phenobarbital and the shorter-acting ones such as amytal, pentobarbital sodium and seconal. Although occasionally some studies have shown them to be partially effective, a careful review of the results obtained reveals that their use in treatment of motion sickness[11] is not justified.

The thiobarbiturates have been studied for the relief of motion sickness because of the possibility that these compounds, many of which have been known to produce actual central nervous stimulation, would be effective in motion sickness yet not produce undue depression. Noble, in the Canadian laboratories, has studied several of these and one of them, ethyl-β-methylallyl thiobarbituric acid, was shown to be moderately effective in swing sickness.[10] Later studies of seasickness and swing sickness[12,13] did not reveal such dramatic results. This thiobarbiturate has a long-continued action and Noble has stressed the value of pretreatment with the drug. This of course would impair its usefulness in airsickness.

Several vitamins have been employed experimentally for the relief of motion sickness and some of them have been incorporated with other drugs. Because of its dilating effect on cerebral vessels, niacin (nicotinic acid) has been employed in mixtures in an attempt to increase the concentration of alkaloids in the cerebral circulation. Some early results in swing sickness led to its adoption as one of the components of the Canadian seasickness remedy, but later studies have failed to confirm the beneficial effects[10] and it is now generally believed that it has not contributed to the effectiveness of this remedy. Thiamine has been demonstrated to be without appreciable effect in swing sickness.[14] Pyridoxine has been used in the treatment of nausea and vomiting of pregnancy[15,16] and the nausea and vomiting associated with radiation sickness.[17] This led to its study in swing sickness but it was not demonstrated to be effective.[18]

In an attempt to overcome the depressing effects on salivation of atropine-like drugs, neostigmine bromide was employed in combination with hyoscine,[12] atropine[13] or syntropan.[13] In no case was the observed protection increased appreciably by the neostigmine.

Many of the drugs proposed for use in airsickness may produce, when given in large doses, sufficiently severe side effects to preclude their use by personnel other than passengers. Of the atropine-like drugs the principal effect is dryness of the mouth associated with the decrease in flow of saliva. This occurs to a significant extent with the more effective atropine-like drugs although the depression of salivary secretion is not closely associated with the effectiveness of the drug in swing sickness.[5] In a study of performance, in which addition and decoding tests were used for testing intelligence and pursuit meters and steadiness tests for testing psychomotor performance, no significant effects were observed after the administration of 0.5 mg. hyoscine hydrobromide[7] either at ground level or at

18,000 feet simulated altitude. Although the near point of accommodation was not affected by any atropine-like drugs in the doses commonly employed, Keil has shown[19] that doses of hyoscine greater than 1.5 mg. produce effects on accommodation and significantly lower visual efficiency in many individuals. Administration of a dose of 1.5 mg. or more would correspond to the simultaneous administration of more than two of the commonly employed doses of hyoscine. Significant deleterious effects on vision were not observed in navigation students either in the Navy[8] or the Army Air Forces[9] when hyoscine was employed for airsickness. These are rather critical groups for such a study since they fly rather long missions and during most of the time are working on charts and instruments that require good near vision. In another study of possible side effects of hyoscine that might be of importance it was found that neither hyoscine nor hyoscyamine had any obvious effect on physical performance, ability to shoot[13] or near vision. Other studies have shown that hyoscine is unlikely to have any deleterious effect due to diminution of sweating unless given to men on the border line of heat stroke.[6]

As is to be expected the ordinary barbiturates may produce considerable central nervous system depression although the doses ordinarily employed are smaller than those commonly used for hypnosis. In a comparative study of the Royal Canadian seasickness remedy (containing hyoscine, hyoscyamine and niacin), the army motion sickness remedy (containing hyoscine, atropine and niacin) and hyoscine alone[13] the effects were placed in two categories: those in which the subjects complained of a hot, dry feeling, dry mouth and bleariness of vision and those in which the primary sensation was that of being doped or drugged with the most common complaint being sleepiness. Most of the complaints of those taking the Canadian seasickness remedy were of the second type with the fewest complaints being made by the group taking hyoscine alone.

An analysis of the effects of drugs on motion sickness suggests that central mechanisms at a cortical level are of no greater importance in airsickness than in other forms of motion sickness. Evidence for this is: (1) the correlation between the effects of various drugs in swing sickness, seasickness and airsickness; (2) the lack of effectiveness in any type of motion sickness of cortical depressants such as barbiturates and chlorobutanol; (3) the failure of epinephrine to increase the susceptibility to motion sickness and (4) the lack of evidence that drugs effective in motion sickness are depressants of the central nervous system. In connection with the last it is common to suppose that hyoscine is a depressant of the central nervous system although in therapeutic doses it is a respiratory stimulant. The evidence on this point is incomplete but observations that mixtures of hyoscine and morphine are depressant are scarcely relevant. It is apparent that since motion sickness is not amenable to therapy in all cases it is quite possible there may be cases in which cortical factors are of decisive importance.

Of all the drugs that have been investigated so far only those of the atropine series are of consistently demonstrated value in the prevention of motion sickness. Of these, hyoscine is the most promising one because of its high degree of effectiveness and relative freedom from undesirable side effects. The dose of hyoscine hydrobromide ordinarily employed is 0.65 to 0.75 mg. repeated not more often than once in six hours. The dose of atropine ordinarily employed is 1.0 mg. with the same time interval elapsing between successive doses. The onset of action of these drugs is approximately one hour.

There is not sufficient evidence of their effectiveness to warrant the use of barbiturates, vitamins or central nervous system stimulants in motion sickness.

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Clinical Studies

Quantitative Estimation of the Albumin and Gamma Globulin in Normal and Pathologic Cerebrospinal Fluid by Immunochemical Methods*

ELVIN A. KABAT, PH.D., MURRAY GLUSMAN, M.D. *and* VESTA KNAUB
New York, New York

BECAUSE of the low protein content of cerebrospinal fluid, the usual chemical methods of fractionation used to measure albumin and globulin in serum are not applicable. Detection of increases in the globulin in cerebrospinal fluid is generally carried out by procedures such as the colloidal gold test[1,2] which does not provide a direct measure of the gamma globulin but depends on the relative proportions of albumin to gamma globulin.[3] Sensitivity of the gold sol used in different laboratories varies greatly and unless the test is carried out by the improved technics of Lange[4] it is of value chiefly in diagnosis of paresis. Whereas electrophoretic studies of cerebrospinal fluid[3] have demonstrated that much of the cerebrospinal fluid protein was derived from the plasma and have provided a direct quantitative measure of the various proteins present, the large quantities of cerebrospinal fluid needed for examination precluded electrophoretic analysis as a routine diagnostic procedure.

The methods of quantitative immunochemistry appear ideally suited for the estimation of such small amounts of protein. Heidelberger and Kendall[5] first used the quantitative precipitin method for the estimation of small quantities of specific polysaccharides and subsequently Goettsch and Kendall[6] applied the procedure to the estimation of albumin and globulin in serum. In subsequent studies the technic was applied to pathologic sera, lymph, ascitic fluid, edema fluid[7,8] and its application to cerebrospinal fluid has been suggested.[9] Data on the amounts of Bence Jones protein in the serum of a patient with multiple myeloma[10] have also been obtained immunochemically. More recently Chow[11] has shown that values for plasma albumin obtained by the quantitative precipitin method were in general agreement with those obtained from electrophoretic analysis. Several authors[12–15] report other applications of immunochemical methods.

The method requires immunization of rabbits with relatively pure preparations of the proteins to be assayed and absorption of the sera to eliminate antibodies other than those to the desired constituent. A calibration curve is then prepared by the addition of increasing quantities of the antigen to a measured volume of antiserum, the precipitates centrifuged off, washed twice in cold saline to remove non-specific protein and analyzed for nitrogen. To assay an unknown cerebrospinal fluid an appro-

* From the Departments of Neurology and Bacteriology, College of Physicians and Surgeons, Columbia University and the Neurological Institute, New York, N. Y. The work reported in this communication was supported by grants from the National Multiple Sclerosis Society and the William J. Matheson Commission.

priate dilution of the fluid is added to another portion of antiserum, the precipitate washed and analyzed and the content of antigen in the volume of diluted fluid added is read off from the calibration curve and the albumin or globulin content of the undiluted cerebrospinal fluid computed; as the method has been developed analyses and calibration curves are valid only in the region of antibody excess.[12–15]

Among the factors which have retarded adoption of the quantitative precipitin method for routine clinical use has been the necessity for the preparation of antigens and antisera. However, large quantities of purified plasma proteins have now become available[16] and it does not seem unreasonable to expect that even specific antisera might become available commercially should the demand warrant.

The present communication outlines the use of the quantitative precipitin method for the estimation of the crystalline serum albumin and gamma globulin in human cerebrospinal fluid. The proportions of albumin and gamma globulin to the total protein have been measured in normal cerebrospinal fluid and in a variety of diseases involving the nervous system. Marked increases in the proportion of gamma globulin were found in the cerebrospinal fluid in a high proportion of cases of multiple sclerosis and in patients with neurosyphilis. In the latter disease the proportion of gamma globulin appeared to correlate generally with the activity of the disease process. In a few cerebrospinal fluids evidence was obtained for an increase in the concentration of protein other than albumin and gamma globulin.

EXPERIMENTAL METHOD

Twice crystallized human serum albumin and purified human gamma globulin prepared in the laboratories of Dr. E. J. Cohn were provided by Dr. E. Brand.

To prepare antigamma globulin and antihuman crystalline albumin groups of rabbits were injected intravenously with alum or protamine precipitated antigen four times a week for four weeks. Each rabbit received a total of about 18 mg. of protein. Five days after the last injection 50 ml. of blood were obtained from each animal by cardiac puncture. Animals were then given similar additional series of injections and bled in the same manner. The serum was separated from the blood by centrifugation in the cold. Stock solutions containing 1 mg. of antigen per ml. were prepared in saline. A drop of toluene was added as a preservative. The nitrogen content of the solutions was determined by the Markham micro-Kjeldahl method.[17]

A rough estimate of the antibody content of the sera was made by the addition of successive, small portions of antigen to 0.5 ml. of serum and centrifuging the precipitate formed after each addition, until no further precipitation occurred. The combined precipitates were then washed twice with cold saline and analyzed for nitrogen. Based on such preliminary analyses several antisera of about the same potency were pooled. It was found necessary to absorb the antiglobulin pools with albumin and the antialbumin pools with globulin. For example, an antiglobulin pool of two bleedings each from two rabbits required three additions of 0.30 mg. albumin N for complete absorption. After absorption saline was added to dilute the serum to a concentration of about 100 to 150 μg. of antibody N per ml. and merthiolate added to a final concentration of 1:10,000.

A calibration curve was prepared by the addition of increasing quantities, as for example, 3, 6, 9, 12, 15, 18, 21 μg. N of the stock solution of antigen to a measured amount of serum, usually 1 ml. in a constant total volume of 3 ml. Each point is set up in duplicate. Two additional tubes containing only serum serve as a control. After one hour in a water bath at 37°C. and forty-eight hours in the refrigerator the precipitates are centrifuged off in a refrigerated centrifuge and washed twice with 3.0 ml. of chilled saline.[5–8] The precipitate is then carefully dissolved in M/2 NaOH and transferred quantitatively to micro-Kjeldahl flasks and analyzed for nitrogen by the Markham micro-Kjeldahl method.[17] The total N in the washed precipitate is plotted against the quantity of antigen added.

The serum supernatants from each point are combined and tested for antibody and antigen. Two ml. of supernatant are pipetted into each of two tubes. To one tube 0.15 ml. of antiserum is

added and to the other approximately 3 μg. of antigen N is added. The tubes are placed at 37°C. for two hours and in the refrigerator overnight, then centrifuged and read. If a precipitate is obtained with antigen, the supernatant contained an excess of antibody; if precipitation occurs on addition of antibody, an excess of antigen is present. The calibration curve is valid only in the region in which antibody is in excess.

Before attempting to assay the albumin and gamma globulin of a spinal fluid it is necessary to know its total protein content so that a dilution may be selected which will give an amount of precipitate falling on the calibration curve. The total protein content is measured turbidimetrically after precipitation with sulfosalicylic acid. For spinal fluid with a total protein of 35 mg per 100 ml., 1 ml. portions may be used for the globulin determination and 1 ml. of a 1:3 dilution for the estimation of albumin. With cerebrospinal fluids of higher protein content proportionately higher, dilutions are chosen. The supernatants from each determination are also tested with antigen and antiserum to verify the presence of excess antibody. Should excess antigen be found, the analysis must be repeated with a higher dilution of cerebrospinal fluid. When some familiarity with the method has been acquired, dilutions which will regularly fall on the calibration curve may be selected without difficulty. With each set of analyses, it is advisable to check one point on the calibration curve for albumin and for globulin.

As carried out the amounts of nitrogen in the precipitates vary from 30 to 150 μg. This range is intermediate between that ordinarily employed for quantitative precipitin assays[5-8] and the micro method developed by Heidelberger and MacPherson.[18] In the latter method, tubes are allowed to remain in the refrigerator for one week. For these studies forty-eight hours was the period of time selected for the preparation of calibration curves and for analysis of unknowns since the method would be of little clinical interest if results required a longer interval. It was noted in comparative experiments that slightly larger amounts of precipitate were found if tubes were left for a week. Since the total antibody content was of no consequence in this work, the uniform use of forty-eight hours for standards and unknowns did not in any way reduce the precision of the results.[15] Validity of the method was checked by the addition of known quantities of albumin or gamma globulin to cerebrospinal fluid and determining the recovery.

RESULTS

Table 1 summarizes data on the total protein, albumin and gamma globulin in the cerebrospinal fluid of ten healthy medical students and twenty-two patients at the Neurological Institute, admitted for various complaints, who had essentially normal spinal fluid proteins and in whom there was no reason to suspect any abnormalities in the spinal fluid protein. Among the healthy medical students, total protein ranged from 25 to 38 mg. per 100 ml., albumin from 11 to 19 and gamma globulin from 1.7 to 3.8 mg. per 100 ml. In the series of patients with presumed normal cerebrospinal fluids, total protein varied from 19 to 54, albumin from 7.6 to 29 and gamma globulin from 1.8 to 6.3 mg. per 100 ml. In the entire group of fluids the albumin to gamma globulin ratios varied from 3.8 to 8.8; the percentages of albumin to total protein and of gamma globulin to total protein from 38 to 62 and from 5 to 13. The crystalline albumin and gamma globulin accounted for from 43 to 75 per cent of the total cerebrospinal fluid protein.

The means and standard deviations[19] for the data in Table 1 were as follows:

	Albumin		Gamma Globulin	
	Mean mg./100 ml.	Standard Deviation	Mean mg./100 ml.	Standard Deviation
Normals	15.9	2.5	2.7	0.65
Patients with proteins of 19–39 mg./100 ml.	14.2	4.0	3.0	0.71
Patients with proteins of 40–54 mg./100 ml.	22.1	3.8	4.5	1.0
All fluids in table	17.2	4.9	3.4	1.1

It is evident that the group of patients with proteins of 19 to 39 mg. per 100 ml. fall into the same range as the ten normal

fluids; the fluids with proteins of 40 to 54 show somewhat elevated values for albumin and globulin as would be expected.

By reference to these values for the means and standard deviations the significance of the values for cerebrospinal fluid albumin and globulin in various neurologic diseases may be evaluated. The probability of significance for values which deviate from the mean by two standard deviations is about 21:1, for two and five-tenths standard deviations about 200 to 1, and for three standard deviations about 369:1.[19]

Table II summarizes data on the albumin and gamma globulin levels of sixteen patients with neurosyphilis. Data on colloidal gold and Wassermann tests on the cerebrospinal fluid sample analyzed are

TABLE I

ALBUMIN AND GAMMA GLOBULIN LEVELS IN THE CEREBROSPINAL FLUID OF HEALTHY INDIVIDUALS AND OF PATIENTS WITH PRESUMED NORMAL SPINAL FLUID PROTEIN

RESULTS OF IMMUNOCHEMICAL DETERMINATIONS

Case No.	Total Protein	Albumin	Gamma Globulin	Albumin + Gamma Globulin	Albumin / Gamma Globulin	Albumin / Total Protein	Gamma Globulin / Total Protein	Albumin + Gamma Globulin / Total Protein	Diagnoses
	mg./100 ml.	mg./100 ml.	mg./100 ml.	mg./100 ml.		%	%	%	
1	25	11	2.2	13	5.0	44	9	53	Healthy medical student
2	31	15	2.6	18	5.8	48	8	56	Healthy medical student
3	32	17	2.8	20	6.1	53	9	62	Healthy medical student
4	32	15	1.7	17	8.8	48	5	53	Healthy medical student
5	32	15	2.7	18	5.6	47	8	55	Healthy medical student
6	33	15	2.8	18	5.4	45	8	53	Healthy medical student
7	36	19	3.8	23	5.0	53	11	64	Healthy medical student
8	37	14	2.0	16	7.0	38	5	43	Healthy medical student
9	38	19	2.6	22	7.3	50	7	57	Healthy medical student
10	38	19	3.8	23	5.0	50	10	60	Healthy medical student
					Presumed Normal Cerebrospinal Fluid				
834566	19	7.4	1.8	9.2	4.1	39	10	49	Cerebral atrophy, cerebral arteriosclerosis, old cerebrovascular accident
866302	20	7.6	1.9	9.5	4.0	38	10	48	Psychoneurosis, conversion hysteria
809111	25	11	2.9	14	3.8	44	12	56	Myasthenia gravis
855976	27	13	2.4	15	5.4	48	9	57	Idiopathic epilepsy
854856	31	14	2.8	17	5.0	45	9	54	Depressive reaction, old fractured skull; mild bilateral cerebral atrophy probably post-traumatic, compression fracture of eighth vertebra post-traumatic
862560	31	15	3.0	18	5.0	48	10	58	Mixed psychoneurosis
844943	31	16	4.1	20	3.9	51	13	64	Acute myasthenia gravis, cortical atrophy, hypertrophied thymus
854637	35	15	3.1	18	4.8	43	9	52	Paralysis of right common perineal nerve, probably traumatic
839702	36	15	3.9	19	3.8	42	11	53	Facial tic, cause undetermined; moderate bilateral cerebral atrophy (more on left)
847411	36	17	3.8	21	4.5	47	11	58	Hypertensive vascular disease, generalized arteriosclerosis, deafness bilateral, cause undetermined
859436	36	16	2.9	19	5.5	45	8	53	Angiospasm; hypertensive cardiovascular disease; cerebrovascular accident, mild
855663	39	23	3.6	27	6.4	59	9	68	Psychoneurosis
850288	40	19	3.6	23	5.3	48	9	57	Syncope, cause undetermined
846347	41	17	3.6	21	4.7	41	9	50	Psychoneurosis, anxiety state; osteoarthritis, carotid sinus syncope?
809649	44	19	4.4	23	4.3	43	10	53	Cerebral atrophy, left, post-traumatic
824809	45	20	5.1	25	4.0	45	11	56	Convulsive disorder, grand mal seizures, secondary optic atrophy
853015	45	22	3.9	26	5.7	49	9	58	Right brachial neuritis, result of old right radical mastectomy; metastatic carcinoma right scapula
850089	47	24	3.3	27	7.2	51	7	58	Torticollis; spastic osteoarthritis cervical spine
852155	47	24	4.5	29	5.3	51	10	61	Sciatic syndrome, cause undetermined
859144	47	29	6.3	35	4.6	62	13	75	Headaches, histamine sensitivity?, psychogenic?
849821	48	19	4.4	23	4.3	40	9	49	Right hemiparesis, birth injury; myositis ossificans
823611	54	28	6.1	34	4.6	52	11	63	Psychoneurosis

also given. Of the seventeen cerebrospinal fluids, ten had total proteins within the range accepted as normal in Table I and in all of these instances the albumin was within the normal range; of the remaining seven fluids with high total proteins, one showed a normal albumin and the remaining six showed somewhat elevated albumins. The most striking changes were found in the amounts of gamma globulin. Sixteen of the seventeen fluids showed a striking increase in the gamma globulin level, the smallest increase being two and two-tenths standard deviations from the mean for fluids in that range of total spinal fluid protein. The gamma globulin values of these sixteen fluids varied from 5.6 to 116 mg. per 100 ml. and the percentage of gamma globulin to total protein from 16 to 82. It is noteworthy that in this group of sixteen the three lowest values for gamma globulin were in the patients who had shown a good response to therapy eight to ten months previously and were improving, had become asymp-

TABLE II

ALBUMIN AND GAMMA GLOBULIN LEVELS IN THE CEREBROSPINAL FLUID OF PATIENTS WITH NEUROSYPHILIS

Case No.	Total Protein	Albumin	Gamma Globulin	Albumin + Gamma Globulin	Albumin / Gamma Globulin	Albumin / Total Protein	Gamma Globulin / Total Protein	Albumin + Gamma Globulin / Total Protein	Colloidal Gold	Spinal Fluid Wassermann	Activity of Disease
	mg./100 ml.	mg./100 ml.	mg./100 ml.	mg./100 ml.		%	%	%			
808655	36	15	5.6	21	2.7	42	16	58	Negative	Negative	Cerebrospinal syphilis, asymptomatic; improved following penicillin and fever eight months previous
832208	44	23	7.5	31	3.1	52	17	69	Negative	+(2 ml.)	Meningovascular syphilis; definitely improved following penicillin and fever ten months previous
848591	41	19	6.7	26	2.8	46	16	62	Negative	Negative*	Neurosyphilis manifested by bilateral optic atrophy; activity questionable
560946	87	34	3.2	37	11	39	4	43	4333221100	++++(0.2 ml.)	Meningovascular syphilis, some improvement
856884	45	14	26	40	0.5	31	58	89	1122211000	++++(0.2 ml.)	Active meningovascular syphilis with involvement of optic nerves
857091	74	40	27	67	1.5	54	36	90	1112211000	++++(0.2 ml.)	Central nervous system lues, vascular type; moderately active, progressing at time of admission
866326	35	19	8.1	27	2.3	54	23	77	Negative	++++(1.0 ml.)	Central nervous system lues, tabes dorsalis, Charcot spine, progression questionable at time of admission
859593	46	22	11	33	2.0	48	24	72	Negative	Negative	Taboparesis, questionably active, recent improvement following penicillin
764893	65	35	17	52	2.0	54	26	80	1122211000	++++(2 ml.)	Juvenile taboparesis, active
871521	68	34	28	62	1.2	50	41	91	2223332110	++++(1 ml.)	Taboparesis active, recent marked improvement following penicillin
862203	78	55	21	76	2.6	70	27	97	Negative	Negative	Central nervous system lues, tabetic, activity questionable, hypertensive cardiovascular disease
853703	68	33	20	53	1.7	49	29	78	Negative	++++(2 ml.)	Central nervous system lues clinical manifestations slight, Ménière's syndrome, diabetes mellitus
	42	24	10.6	35	2.3	57	25	82	Negative	++++(2 ml.)	(Sample twenty-four days later after 9,000,000 units penicillin)
851022	42	15	17	32	0.9	36	40	76	2222100000	++++(2 ml.)	Active general paresis; some improvement following penicillin and fever
863603	48	16	14	30	1.1	33	29	62	Negative	++++(1 ml.)	Active general paresis; received penicillin five months previous
857499	49	15	33	48	0.5	31	67	98	3222110000	++++(0.2 ml.)	Early, moderately active general paresis
852151	141	24	116	140	0.2	17	82	99	Negative	++++(0.2 ml.)	Active general paresis

* Serum Kline ++++.

tomatic, or had a process of questionable activity. In this respect determination of cerebrospinal fluid gamma globulin offers promise as an indicator of the effectiveness of antiluetic therapy. All sixteen fluids showed albumin to gamma globulin ratios in that the sum of the albumin and gamma globulin accounted for only 37 of the 87 mg. of protein in the fluid. This unusually low recovery, together with the finding of a paretic colloidal gold curve, indicates the presence of a considerable amount of a

TABLE III

ALBUMIN AND GAMMA GLOBULIN LEVELS IN THE CEREBROSPINAL FLUID OF PATIENTS WITH DISSEMINATED ENCEPHALOMYELITIS AND MULTIPLE SCLEROSIS

Case No.	Total Protein	Albumin	Gamma Globulin	Albumin + Gamma Globulin	Albumin / Gamma Globulin	Albumin / Total Protein	Gamma Globulin / Total Protein	Albumin + Gamma Globulin / Total Protein	Colloidal Gold	Diagnoses and Activity of Disease
	mg./ 100 ml.	mg./ 100 ml.	mg./ 100 ml.	mg./ 100 ml.		%	%	%		
740229	17	6.5	1.3	7.8	5.0	38	8	46	Negative	Acute disseminated encephalomyelitis due to pertussis vaccine, beginning recovery from acute episode
866335	23	8.8	2.1	10.9	4.2	38	9	47	Negative	Acute disseminated encephalomyeloradiculitis, rapid onset, marked activity, some improvement in hospital
848899	51	22	3.6	26	6.2	44	7	51	Negative	Multiple sclerosis, very slowly progressive, seventeen years' duration
853494	26	14	3.1	17	4.5	54	12	66	Negative*	Multiple sclerosis, mild to moderate severity, moderately progressive, three years' duration
868189	35	19	3.1	22	6.1	54	9	63	Negative	Multiple sclerosis, moderately severe, moderately progressive, six years' duration
817816	32	8.6 9.0	4.5 3.8	13.1 12.8	1.9 2.4	27 28	14 12	41 40		Multiple sclerosis, slight improvement in moderately active case
863801	39	19	5.6	25	3.4	49	14	63	Negative	Multiple sclerosis, moderately severe, moderately progressive, six years' duration
864977	26	12	3.8	16	3.2	46	15	61	Negative*	Multiple sclerosis, mild, slight activity, four years' duration
864707	27	11	4.1	15	2.7	41	15	55	Negative	Multiple sclerosis, fairly early, mild, slight improvement
835706	39	20	6.0	26	3.3	51	15	66	Negative	Multiple sclerosis, improved following exacerbation
859087	48	21	8.5	29	2.5	44	18	62	Negative	Multiple sclerosis, mild severity, mild exacerbation, seven years' duration
864021	37	16	7.9	24	2.0	43	21	64	*	Multiple sclerosis, mild to moderate severity, apparently in remission, eighteen years' duration
915 (Albany)†	48	25	12	37	2.1	52	25	77	*	Multiple sclerosis
774971	48	22	15	37	1.5	45	31	76	Negative	Multiple sclerosis, moderate severity, slowly progressive, four years' duration
860909	34	12	11	23	1.1	35	32	68	1122211100	Multiple sclerosis, mild; moderate activity, progressive; two years' duration
857874	38	15	13	28	1.2	40	34	74	1122100000*	Multiple sclerosis, moderate severity, moderately active, two and one-half years' duration

* Typical paretic colloidal gold curves were found in these fluids by Drs. C. Lange and A. H. Harris by their more delicate procedure.[4]
† Fluid supplied by Drs. Lange and Harris.

considerably lower than any of the fluids in Table I. Since ten of the seventeen fluids were negative in the usual colloidal gold test which depends upon the albumin as well as the gamma globulin level,[3] the present method would appear to be more sensitive.

The seventeenth fluid (No. 560,946) showed a normal gamma globulin and a slightly elevated albumin, but was unusual protein other than albumin and gamma globulin. From the low gamma globulin value it is very unlikely that the gamma globulin could be responsible for the paretic colloidal gold curve.[1–3]

Table III summarizes data obtained in two cases of disseminated encephalomyelitis and fourteen cases of multiple sclerosis. The patients with disseminated encephalomyelitis showed essentially normal values for

spinal fluid albumin, gamma globulin and total protein. All of the fourteen patients with multiple sclerosis showed total protein levels within the range accepted as normal in Table 1. Of these, all but one showed essentially normal albumins; the exception gamma globulin values three or more standard deviations from their corresponding means. Of the eleven fluids tested, all but the two fluids with the highest gamma globulin levels showed negative colloidal gold tests as carried out in the usual manner.

TABLE IV

ALBUMIN AND GAMMA GLOBULIN LEVELS IN THE CEREBROSPINAL FLUID OF PATIENTS WITH VARIOUS NEUROLOGIC DISEASES

Case No.	Total Protein	Albumin	Gamma Globulin	Albumin + Gamma Globulin	Albumin / Gamma Globulin	Albumin / Total Protein	Gamma Globulin / Total Protein	Albumin + Gamma Globulin / Total Protein	Diagnoses
	mg./100 ml.	mg./100 ml.	mg./100 ml.	mg./100 ml.		%	%	%	
852380	36	14	3.3	17	4.2	39	9	48	Amyotrophic lateral sclerosis
847446	38	19	3.1	22	6.1	50	8	58	Amyotrophic lateral sclerosis
851254	70	30	5.3	35	5.7	43	8	51	Amyotrophic lateral sclerosis
857377	33	18	2.9	21	6.2	55	9	64	Pernicious anemia; subacute combined degeneration
854387	32	14	12	26	1.2	44	38	82	Degenerative cord disease
850392	39	26	5.3	31	4.9	67	14	81	Degenerative cord disease
856878	64	33	7.0	40	4.8	52	11	63	Herniated nucleus pulposus
853265	100	56	15	71	3.7	56	15	71	Herniated nucleus pulposus
846548	106	61	17	78	3.7	58	16	74	Acute anterior poliomyelitis
854040	400	172	61	233	2.8	43	15	58	Acute anterior poliomyelitis
849428	55	28	6.8	35	4.0	51	12	63	Myoclonus epilepsy
845614	35	16	3.1	19	5.1	46	9	55	Paralysis agitans, arteriosclerotic
854591	53	35	5.0	40	7.0	66	9	75	Paralysis agitans, generalized arteriosclerosis; arteriosclerotic heart disease; diabetes mellitus
862302	47	27	5.5	33	4.9	57	12	69	Presenile psychosis; cerebral arteriosclerosis; mastoiditis chronic
845101	63	31	5.0	36	6.2	49	8	57	Generalized and cerebral arteriosclerosis
842927	20	7.9	2.9	10.8	2.6	40	15	55	Pituitary adenoma
829778	38	19	5.1	24	3.7	50	13	63	Pituitary chromophobe adenoma; bilateral cervical ribs
844137	42	20	3.9	24	5.1	48	9	57	Oligodendroglioma (right lateral ventricle) verified by operation
	39	18	3.2	21	5.6	46	8	54	Oligodendroglioma (sample taken fourteen days after first)
844971	258	114	50	164	2.3	44	19	63	Left frontal lobe abscess (communicating with the ventricular system) demonstrated by operation; basal meningitis, organism undetermined
848484	108	35	9.7	45	3.6	32	9	41	Basilar and spinal leptomeningitis chronic; secondary hydrocephalus probably result of suppurative leptomeningitis; organism undetermined
759207	96	43	6.9	50	6.2	45	7	52	Chronic encephalitis
841765	800	410	244	653	1.7	51	31	82	Cryptococcus hominis neoformans; leptomeningitis with focal encephalitis (autopsied)
	980	480	294	774	1.6	49	30	79	
768060	420	220	46	268	4.8	53	13	66	Cryptococcus hominis neoformans meningitis
863998	126	65	13	78	5.0	52	10	62	Guillain-Barré syndrome
838446	164	101	35	136	2.9	62	21	83	Guillain-Barré syndrome
852435	165	97	22	119	4.4	59	13	72	Guillain Barré syndrome
	80	45	10	55	4.5	56	13	69	Guillain Barré syndrome (sample of fluid seven days later)
862444	296	141	38	179	3.7	48	13	61	Guillain Barré syndrome
853710	330	191	56	247	3.4	58	17	75	Guillain Barré syndrome

(No. 817,816) was somewhat low in albumin. With respect to their content of gamma globulin, three patients had levels within one standard deviation from the mean for their range of total protein, the values in three others were between one and two standard deviations higher than the mean, and the remaining eight had

However, Drs. Carl Lange and A. H. Harris, at Albany, assayed five of the fluids by their more sensitive procedure[4] and the fluids were found to give definite paretic curves. Eleven of the fourteen fluids had albumin to gamma globulin ratios below the lowest of the fluids in Table 1 and the percentage of gamma globulin was higher

in ten of the fluids than the highest corresponding value in Table I. Fluid No. 817,816 was unusual in that the albumin and gamma globulin accounted for only 13 to 14 of the 32 mg. of protein, again suggesting the presence of increased quantities of some other protein. (No. 560,946, Table II.) The two sets of values represent repeated determinations on the same sample of fluid and provide an indication of the reproducibility of the method. Data on the activity of multiple sclerosis are included, but no correlation between the phase of the disease and the spinal fluid gamma globulin is as yet apparent.

Data on the spinal fluid proteins in a variety of other neurologic disorders are given in Table IV. Two of three patients with amyotrophic lateral sclerosis showed normal total protein and albumin and gamma globulin values; the third had a high total protein but the proportions of albumin and gamma globulin were normal. Essentially normal values were also found in one patient with pernicious anemia with subacute combined degeneration, one with oligodendroglioma, two with pituitary adenomas and in two of four patients with arteriosclerosis. Of the remaining two patients one showed a high total protein (845,101) and the other a high albumin (854,591). One of two patients with degenerative cord disease showed a marked increase and the other a slight rise in gamma globulin. Two subjects with herniated nucleus pulposus showed an increase in total protein and the albumin and gamma globulin were also correspondingly increased. Similar findings were also noted in two patients with poliomyelitis. The remaining cases comprise those with fluids with very high total proteins. In these instances there is, as previously pointed out from electrophoretic data,[3] chiefly an increase in all of the spinal fluid proteins. However, one of two patients with meningitis due to Cryptococcus hominis, one with cerebral abscess and two of six patients with Guillain-Barré syndrome showed increases in the proportion of gamma globulin.

COMMENTS

The immunochemical methods employed in these studies provide a direct measure of the quantities of albumin and gamma globulin in cerebrospinal fluid on a weight basis. When combined with determinations of the total protein of the cerebrospinal fluid, the three values enable differences in proportions of these constituents to be readily established. In addition, an indication of changes in proteins other than albumin and gamma globulin may be obtained by difference. Results, in general, confirm and extend those previously obtained by electrophoresis.[3] Although the same fluids were not examined by both methods, the values for albumin and gamma globulin for presumed normals[3] calculated from electrophoretic patterns are in general agreement with the values reported above. While the quantities of fluid required for electrophoretic analysis are so large as to preclude its routine diagnostic use even when the Tiselius apparatus is available, the present method requires at most but 6 or 7 ml. of cerebrospinal fluid for duplicate albumin and gamma globulin determinations and estimation of total protein. Among other advantages are that a number of analyses may be carried out at the same time and that specialized apparatus is not required. If a refrigerated centrifuge is not available, a small centrifuge placed in an icebox or cold room is adequate. As described, about three days is the minimum time between receipt of the sample and completion of the analyses. The method, unlike the salt-fractionation procedures, is not affected by the total protein concentration and is specific for the constituents to be measured. The absorbed antialbumin and antigamma globulin sera did not react with fibrinogen and, since supernatants from the calibration curves and the spinal fluids did not show a zone in which both antibody and antigen were present, it is reasonable to infer that each absorbed antiserum contained antibody only to the antigen which it was desired to estimate.[8,12,13,14,15,20]

In addition, the same values were obtained when a given spinal fluid was analyzed with several calibrated antisera. Further evidence that the absorbed antisera were specific was obtained by the technic of Ovdin[21] in which human serum was layered over agar gels containing the respective absorbed antisera. As diffusion into the gel took place only a single bond of specific precipitate was observed with each antiserum corresponding to that obtained by layering the antigen used in preparing the antiserum over a similar agar gel. No bond was observed with the heterologous antigen. Although it is more involved than the colloidal gold test, it provides values which are independent of the other proteins present.

The results indicate that the method is of greatest value with those cerebrospinal fluids with normal or somewhat elevated total protein levels in that it provides information about changes in the relative proportions of the constituents. With fluids with very high total protein (above 200), it has thus far provided very little additional information of clinical significance.

It is evident that definite increases in the absolute amount and in the percentage of gamma globulin occurred in the cerebrospinal fluid of those with neurosyphilis (Table II) and in a large proportion of patients with multiple sclerosis. (Table III.) Patients with active neurosyphilis showed extraordinarily elevated gamma globulins while those individuals who had been treated successfully or who did not show evidence of activity had gamma globulins which were much lower and presumably were returning to normal. It would appear that estimation of spinal fluid gamma globulin may be of value as a guide in evaluating antiluetic therapy.

Findings of a significantly increased gamma globulin in eight of fourteen patients with multiple sclerosis and of an increase in the percentage of gamma globulin to total protein in ten of these patients strongly suggests the usefulness of this test in helping to establish the diagnosis of multiple sclerosis, a diagnosis which is not infrequently quite difficult to make with certainty. Present data are not sufficient to establish the relation between the stage of the disease and the gamma globulin level. Further studies are contemplated in which a group of patients will be followed over a considerable period to elucidate this point. It is perhaps significant that the two patients with acute disseminated encephalomyelitis showed normal albumin and globulin values.

SUMMARY

1. An immunochemical method for the estimation of albumin and gamma globulin in cerebrospinal fluid is outlined.

2. Normal values for albumin and gamma globulin are presented.

3. In fifteen of sixteen cases of neurosyphilis, increases in gamma globulin were found. The highest values were found in those patients with active neurosyphilis and the lowest in patients who had shown a favorable response to therapy.

4. Eight of fourteen patients with multiple sclerosis showed an increased spinal fluid gamma globulin.

5. Data on cerebrospinal fluid albumin and gamma globulin in a variety of other diseases are presented.

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Serum Proteins in Syphilis*

Electrophoretic Study

EARL P. BENDITT, M.D. *and* SHELDON A. WALKER, M.D.

Chicago, Illinois

THE Tiselius method of electrophoresis[16] offers a tool with which to investigate certain properties of colloidal mixtures including the serum proteins. The method has been used to study serum proteins in many diseases and interesting changes have been found.[6,8,15] The physiologic and pathologic significance of these findings remains in large part to be worked out.

It has been stated that in syphilis there are changes in the electrophoretic pattern of the serum proteins which are "characteristic and statistically significant."[3] These changes consisted in an "increase in all of the electrophoretic globulin fractions." Others[11] demonstrated the changes in this disease to be of a more limited nature and to consist of a decrease in albumin and an increase in gamma globulin. Similar alterations were found in biologic false-positive sera.

The present studies were undertaken in order to (1) re-examine the electrophoretic pattern changes in syphilis, (2) to correlate the pattern alterations with the stage of the disease, the effects of treatment and other possible influencing factors and (3) further evaluate the use of electrophoresis as an aid in the serologic diagnosis of syphilis.

METHODS AND MATERIALS

Patients in this study were derived mainly from the clientele of the University of Chicago Clinics. Those with primary disease were from the Chicago Intensive Treatment Center. An attempt was made to obtain serum from patients who had (1) a definite diagnosis of syphilis on evidence other than serologic tests, (2) patients in all stages of the disease, and (3) patients with and patients without previous treatment. A small group of patients was studied in whom the serologic tests were positive, but in whom there was some reason to doubt the presence of syphilis. They were followed until it was decided definitely that there was no syphilis present. Control sera were obtained from healthy men and women of the Clinics staff. Only those without recent acute infections were used.

Blood was drawn in the morning before breakfast. It was allowed to clot at room temperature for several hours and the serum separated by centrifugation. Sera were stored in the frozen state at $-15°$C. We have tested the acute effects of freezing and thawing upon both human and rat sera and have found no alteration beyond the limits of experimental error.

Four milliliters of serum were dialysed against 2 liters of buffer for a minimum of forty-eight hours at 4°C. The buffer was composed of 0.100 moles of sodium diethylbarbiturate, and 0.020 moles of diethylbarbituric acid per liter of solution.[9] The ionic strength of this buffer is 0.1 and the pH 8.6. At the end of dialysis the serum was diluted to 12.0 milliliters by the addition of the requisite amount of buffer.

Electrophoresis was carried out in a double section Tiselius cell.[16] The apparatus used varied slightly from the usual design in that the schlieren and camera lenses had a focal length of 38 cm. The optical system was otherwise of the type described by Philpot.[12] The potential gradient was approximately 8 volts per cm. and the bath temperature 1°C. Runs were of seventy to eighty-minutes' duration. It has been shown that adequate separation for measurement can be achieved after sixty minutes at a potential gradient of 6.5 volts per cm.[4]

* From the Department of Pathology and the Section of Dermatology, Department of Medicine, University of Chicago, Chicago, Ill.

Patterns were enlarged five diameters and traced. The individual components were separated by vertical lines drawn from the minima of the curves to the baseline. Area measurements were made with a planimeter. Both ascending and descending limb patterns from each analysis were measured. The values for each component were averaged except in the case of beta globulin. Because of the descending limb beta boundary anomaly, only the ascending area was used for this component.

An estimate of the error in the method was made as follows: Assuming that with a given electrophoresis apparatus the same sample of serum will produce the same pattern each time it is separated under the same conditions, then the error in the determination lies in the reproducibility of the enlarged pattern tracings, the delineation of the components and their measurement with the planimeter. Duplicate tracings and measurements were made on thirteen individual patterns by two observers. The coefficient of variation for the total pattern area was found to be ± 1.71 per cent. Computed on the basis of serum protein concentration (for an average value of 7.0 Gm. per cent) the error is ± 0.12 Gm. per cent. Errors in the individual components were all of a similar order of magnitude and varied between ± 0.04 and ± 0.08 Gm. per cent.

Protein concentration was estimated by determining the protein nitrogen of the serum by micro-Kjeldahl and using the factor 6.25.

Serologic tests were done in most instances on the same serum used for electrophoresis; in the remainder the tests were done on sera drawn

TABLE I

ELECTROPHORETIC DATA FOR NORMAL HUMAN SERA

Case No.	Sex	Age	% Composition					Component Concentration Gm. %					
			Alb.	α_1	α_2	β	γ	Alb.	α_1	α_2	β	γ	TP
Normal Males													
N1	M	24	60.6	5.4	9.4	14.7	9.8	4.16	0.37	0.65	1.01	0.67	6.86
N2	M	31	55.7	4.6	8.7	18.4	12.7	4.16	0.35	0.65	1.37	0.95	7.47
N3	M	22	56.3	4.5	9.8	16.8	12.6	3.96	0.32	0.69	1.18	0.89	7.04
N4	M	22	57.5	5.7	10.2	18.3	8.3	4.07	0.40	0.72	1.29	0.59	7.07
N5	M	17	57.2	4.6	8.9	14.3	15.0	3.96	0.32	0.62	0.99	1.04	6.93
Mean	..	..	57.5	5.0	9.4	16.5	11.7	4.06	0.35	0.67	1.17	0.83	7.07
S.D.	..	..	1.90	0.55	0.80	1.94	2.64	0.100	0.034	0.039	0.168	0.19	0.237
Normal Females													
N6	F	24	61.3	3.7	9.1	13.1	12.8	4.45	0.27	0.66	0.95	0.93	7.26
N7	F	33	54.4	5.5	10.6	17.5	12.0	3.36	0.34	0.65	1.08	0.74	6.17
N8	F	36	60.1	4.3	8.3	13.5	13.9	3.95	0.28	0.54	0.89	0.91	6.57
N9	F	21	52.7	4.1	10.7	14.5	17.9	4.04	0.31	0.82	1.11	1.37	7.65
N10	F	20	59.6	4.2	7.7	14.0	14.6	4.28	0.30	0.55	1.01	1.05	7.19
N11	F	23	60.6	5.7	7.9	13.7	12.0	3.85	0.36	0.50	0.87	0.76	6.34
N12	F	21	60.3	4.6	8.6	14.0	12.5	3.75	0.29	0.53	0.87	0.78	6.22
Mean	..	..	58.4	4.6	9.0	14.3	13.7	3.95	0.31	0.61	0.97	0.93	6.77
S.D.	..	..	3.41	0.74	1.23	1.47	2.10	0.357	0.032	0.112	0.101	0.222	0.588
Combined Normals													
Mean	..	..	58.0	4.7	9.2	15.2	12.8	4.00	0.32	0.63	1.05	0.89	6.90
S.D.	..	..	2.81	0.67	1.00	1.95	2.45	0.276	0.039	0.091	0.162	0.207	0.483

Protein concentration was estimated by determining the protein nitrogen of the serum by micro-Kjeldahl and using the factor 6.25.

Serologic tests were done in most instances on the same serum used for electrophoresis; in the remainder the tests were done on sera drawn

within a few days of that used for fractionation. Multiple serologic examinations were done on all patients. Tests were run either in the laboratory of the Chicago Intensive Treatment Center or the Serology Laboratory of the University of Chicago Clinics. Kahn tests were done on all sera; the Wassermann test was done on all except those who had primary lesions. The Treponema pallidum was demonstrated in all of the primary lesions by dark field examination.

EXPERIMENTAL OBSERVATIONS

The essential clinical and electrophoretic data for normal controls, untreated and treated syphilitic patients, respectively, are

TABLE II

CLINICAL AND ELECTROPHORETIC DATA FOR UNTREATED SYPHILITIC PATIENTS

Case No.	Sex	Age	Duration of Disease	Clinical Signs	Serology	Complications	% Composition					Component Concentration Gm. %					
							Alb.	α_1	α_2	β	γ	Alb.	α_1	α_2	β	γ	TP
Primary Syphilitics																	
P1	F	19	6 days	+	Pos.	0	50.1	5.0	9.8	16.2	18.9	3.44	0.34	0.67	1.11	1.29	6.86
P2	F	18	14 days	+	Pos.	0	43.1	5.9	11.2	12.7	27.2	3.15	0.43	0.82	0.92	1.99	7.31
P3	M	27	7 days	+	Neg.	0	59.1	3.4	8.8	14.7	14.1	4.47	0.25	0.66	1.11	1.07	7.86
P4	F	17	7 days	+	Pos.	+*	45.5	5.1	10.2	12.3	27.0	3.53	0.39	0.79	0.95	2.09	7.75
P5	F	18	?	+	Neg.	+†	46.2	5.2	9.8	15.6	23.2	3.67	0.41	0.78	1.24	1.84	7.94
Mean	..	..	.....	..	....	..	48.8	4.9	10.0	14.3	22.1	3.65	0.36	0.74	1.07	1.66	7.54
S.D.	..	..	. ..	..	....	..	6.28	0.92	0.87	1.73	5.60	0.495	0.072	0.074	0.131	0.451	0.425
Secondary Syphilitics																	
S1	F	23	?	+	Pos.	+‡	39.4	8.5	15.6	17.3	19.2	2.78	0.60	1.10	1.22	1.35	7.05
S2	F	22	4 mo.	+	Pos.	0	48.7	6.4	10.3	14.4	20.2	3.54	0.47	0.75	1.04	1.47	7.26
S3	F	19	5 mo.	+	Pos.	0	48.6	4.5	8.8	14.5	23.6	3.70	0.34	0.66	1.10	1.80	7.61
S4	M	42	3 mo.	+	Pos.	0	42.8	7.8	14.9	16.2	18.2	2.68	0.49	0.93	1.01	1.14	6.25
S5	F	23	?	+	Pos.	0	50.2	4.4	14.1	14.9	16.4	3.55	0.31	1.00	1.05	1.16	7.07
S6	M	26	48 days	+	Pos.	0	57.1	6.4	9.5	13.3	13.7	4.15	0.47	0.69	0.97	1.00	7.28
Mean	..	..	.....	..	....	..	47.8	6.3	12.2	15.1	18.6	3.40	0.45	0.86	1.07	1.32	7.09
S.D.	..	..	.....	..	....	..	6.16	1.67	3.00	1.43	3.38	.345	.106	.181	.087	.288	.457
Tertiary Syphilitics																	
T1	M	67	25 yr.	+	Pos.	+§	49.1	6.9	11.9	13.8	18.2	3.38	0.47	0.82	0.95	1.25	6.87
T2	M	56	15 yr.	+	Pos.	0	51.8	3.6	10.7	18.9	15.0	3.63	0.25	0.75	1.32	1.05	7.00
T3	M	57	?	+	Pos.	0	50.6	4.9	9.0	16.1	19.5	3.68	0.35	0.65	1.17	1.41	7.26
T4	M	42	19 yr.	+	Pos.	0	46.6	5.0	12.6	16.2	19.7	3.39	0.36	0.92	1.18	1.44	7.29
Mean	..	..	.....	..	....	..	49.5	5.0	11.0	16.2	18.1	3.52	0.36	0.78	1.16	1.29	7.10
S.D.	..	..	.....	..	....	..	2.24	1.35	1.58	2.09	2.17	0.157	0.090	0.114	0.153	0.179	0.202
Congenital Syphilitic																	
C1	F	13	13 yr.	0	Pos.	0	57.6	5.4	8.3	11.8	16.9						

* Gonorrhea
† Chancroid
‡ Eleven days post partum
§ Arteriosclerosis; hypertension

found in Tables I, II and III. Electrophoretic data are presented both as percentage composition of the pattern and as concentration in Gm. per cent of the individual components. In Table IV are the data for

by others[2] that these are not significantly altered. The general configuration of all the patterns is not markedly different, and the descending beta globulin anomaly is present in all cases.

TABLE III

CLINICAL AND ELECTROPHORETIC DATA FOR TREATED SYPHILITIC PATIENTS

Case No.	Sex	Age	Duration of Disease	Clinical Signs	Serology	Complications	Duration of Treatment	% Composition					Component Concentration Gm. %					
								Alb.	α_1	α_2	β	γ	Alb.	α_1	α_2	β	γ	TP
Secondary Syphilitics																		
ST1	F	38	1½ yr.	+	Pos.	+†	2 wk.	51.0	5.8	10.2	20.3	12.7	3.44	0.39	0.69	1.37	0.86	6.75
ST2	M	26	2 mo.	+	Pos.	0	8 days	57.7	5.5	8.9	15.2	12.7	4.52	0.43	0.70	1.19	1.00	7.84
ST3	F	23	?	+	Pos.	0	8 days	50.6	5.0	12.4	16.1	15.9	3.39	0.33	0.83	1.08	1.06	6.69
ST4	F	36	3 yr.	+	Pos.	0	1½ yr.	50.6	5.1	9.3	18.6	16.3	3.73	0.38	0.69	1.37	1.20	7.39
ST5	M	26	2 yr.	0	Neg.	0	2 yr.	59.2	4.4	8.3	15.6	12.5	4.09	0.30	0.57	1.08	0.86	6.92
Mean								53.8	5.2	9.8	17.2	14.0	3.83	0.37	0.70	1.22	1.00	7.12
S.D.								6.35	0.79	2.24	3.28	2.84	0.706	0.076	0.137	0.217	0.214	0.728
Tertiary Syphilitics																		
TT1	F	33	?	0	Pos.	0	8 mo.	54.8	4.9	10.1	17.7	12.5	3.71	0.33	0.69	1.20	0.84	6.77
TT2	M	61	5 yr.	+	Pos.	0	1 yr.	52.3	3.6	9.4	14.6	10.1	3.74	0.22	0.56	0.87	0.61	6.00
TT3	M	68	26 yr.	+	Pos.	+‡	2 mo.	52.9	4.3	10.4	16.8	15.6	3.91	0.32	0.77	1.24	1.15	7.40
TT4	F	39	?	0	Pos.	0	4 yr.	58.8	3.7	9.1	15.1	13.4	4.79	0.30	0.74	1.23	1.09	8.16
TT5	F	48	13 yr.	+	Pos.	0	5 yr.	62.1	3.9	8.4	14.5	11.1	4.22	0.27	0.57	0.98	0.75	6.79
TT6	M	46	1 yr.*	+	Pos.	0	1 yr.	46.3	6.5	14.4	14.9	17.8	3.04	0.43	0.95	0.98	1.17	6.57
TT7	F	22	3 yr.	0	Pos.	0	3 yr.	56.1	5.4	10.8	12.4	15.3	3.82	0.37	0.74	0.84	1.04	6.81
TT8	F	52	30 yr.	+	Neg.	0	3 yr.	48.1	7.2	11.4	18.5	14.8	3.70	0.55	0.87	1.42	1.14	7.69
TT9	F	56	12 yr.	+	Pos.	0	1½ yr.	57.7	3.8	8.0	13.4	16.9	3.66	0.24	0.51	0.85	1.07	6.35
Mean								55.5	4.8	10.2	15.3	14.2	3.84	0.34	0.71	1.07	0.98	6.95
S.D.								5.64	1.32	1.92	1.99	2.59	0.471	0.103	0.146	0.209	0.180	0.681
Congenital Syphilitics																		
CT1	M	28	28 yr.	+	Neg.	0	16 yr.	61.5	4.2	7.8	12.5	13.9	3.96	0.27	0.50	0.81	0.90	6.45
CT2	M	7	7 yr.	+	Pos.	0	5 yr.	58.2	4.0	8.4	11.5	17.9	3.71	0.25	0.54	0.73	1.14	6.37

* Premature tertiary lesions
† Pregnancy
‡ Arteriosclerosis; hypertension

three patients with biologic false-positive sera.

Figure 1 presents eight representative serum electrophoretic patterns from controls and patients in all stages of the disease. As can be seen no new components are evident, nor are there any gross alterations in mobilities apparent. Mobilities were not computed from the data, but it has been shown

Control Sera. Determinations were made on twelve normal human sera. Five were from males and seven from females. It is evident (Table I) that the concentrations of alpha-1 and beta globulins are slightly lower in the females. The difference is of borderline significance statistically. A larger series would be necessary to define this difference. Otherwise the patterns appeared

identical in composition. The mean values for the combined normal series were used in the statistical comparisons with the various groups of pathologic sera. Differences were considered "significant" if the statistical probability of their being real was greater than 95 out of 100 (i.e., P less than .05).

TABLE IV

ELECTROPHORETIC DATA FOR PATIENTS WITH FALSE-POSITIVE SEROLOGY

Case No.	Sex	Age	Symptoms or Signs	Serology	Spinal Fluid	Treatment	% Composition					Component Concentration Gm. %					
							Alb.	α_1	α_2	β	γ	Alb.	α_1	α_2	β	γ	T
Q3	F	42	Recent nerve deafness	Neg. to 4+ to Neg.	Neg.	0	52.58	6.50	11.29	17.66	11.98	3.72	0.46	0.80	1.25	0.85	7.07
Q4	F	23	Pregnant	3+ to Neg.		0	55.37	5.66	12.22	14.37	12.37	3.18	0.33	0.70	0.83	0.71	5.75
Q7	F	48	Neuralgia maxillary nerve	1+ to 3+ to Neg.	Neg.	(1938) 8 mo.	48.04	4.92	9.52	23.01	14.52	3.18	0.33	0.63	1.52	0.96	6.62

Untreated Syphilis. The most striking deviation from the normal in the syphilitic sera is the fall in albumin. It is apparent in the primary stage of the disease and remains in the secondary and tertiary stages. The change is evident in both the relative percentage and in the concentration.

The alpha-1 globulin deviates from the normal significantly only in secondary syphilis in which it appears elevated. The alpha-2 globulin is significantly increased in both the secondary and tertiary untreated syphilitics. Beta globulin is not significantly altered in any stage of the untreated disease. In all stages of untreated syphilis the gamma globulin is significantly elevated. Total protein concentration does not vary significantly from the normal in any stage of the disease.

Effect of Treatment. Treated secondary and tertiary syphilitics show only small deviations from the normal in their electrophoretic serum components. These differences are not statistically significant.

Serologic Reaction vs. Altered Serum Protein Fractions. Two of the patients in the untreated group had negative serologic reactions. Both of these were cases of primary disease. One of them (P-3) had a normal electrophoretic pattern, the other (P-5) had marked changes of the characteristic type. The latter patient also had chancroid which may have influenced the pattern.

Not all of the patients with positive serologic reactions have electrophoretic patterns which deviate significantly from the normal. This is particularly evident in the treated patients, of whom ten of the total of twelve have positive serologic reactions, but on the average there is no significant deviation from the normal in their patterns.

Congenital Syphilis. Only three sera were available for study. Two of these were from treated patients and one from an untreated patient. In none of these cases is there any marked deviation from the normal.

Positive Serologic Reaction without Syphilis. In Table IV are the data for three persons who had positive serologic reactions at the time the sera for electrophoresis were collected. These were all declared non-syphilitic on clinical evidence after a follow-up period of one year. In addition, in all patients, the Wassermann reaction eventually reverted to negative spontaneously. These patterns deviate from the normal principally in having low albumin values. Cases Q-3 and Q-4 had elevated alpha-2 globulins and case Q-7 had a markedly

elevated beta globulin. In none of these patients did the gamma globulin deviate significantly from the normal.

Other Factors. The relatively small number of patients examined from the electrophoretic standpoint precluded the possibility of evaluating such factors as the duration of treatment, age and sex on the electrophoretic pattern changes.

None of the patients included in the present series had clinical evidence of lymphopathia venereum. Frei tests were done on ten patients of the group. All were negative.

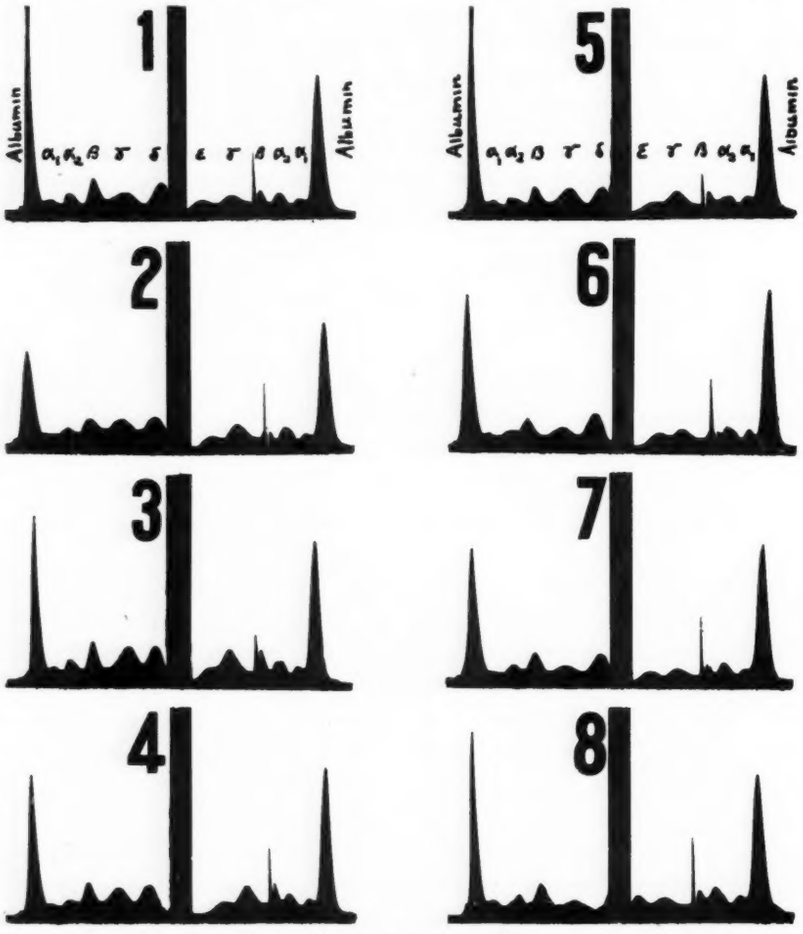

FIG. 1. Representative electrophoretic patterns. The ascending limb is to the left and the descending limb to the right in each pattern set. (1) normal, (2) untreated primary, (3) untreated secondary, (4) untreated tertiary, (5) congenital, (6) treated secondary, (7) treated tertiary and (8) biologic false-positive serum.

COMMENTS

The changes here observed in the electrophoretic patterns of syphilitic sera are similar to those observed by Neurath,[11] the full data for which have recently been published by G. R. Cooper and others.[2] They cannot be directly compared with the findings of J. A. Cooper[3] because of a difference in the methods of expressing globulin values. Using the ratio of each globulin fraction to albumin rather than to total protein in his computations, J. A. Cooper concluded that there was an increase in all of the electrophoretic globulin fractions. If the data of G. R. Cooper and the present observations are expressed in these terms, all globulin values appear likewise to be elevated. This method of expressing electrophoretic results, although frequently used, leads to erroneous conclusions. The

reason for this is easily seen. Ratios of globulin: albumin can change because of variation in the globulins, the albumin or in both. Thus in the case in which all the globulins remain the same but the albumin is decreased, the globulin: albumin ratios will all appear elevated. Such is essentially the situation in the electrophoretic patterns of untreated syphilitics. This explains the apparent discrepancies in the published data on syphilitic sera noted above.

In addition to the changes which have already been described the present investigations bring to light several things which have not previously been mentioned. Most striking is the return of the pattern toward normal with treatment. This occurred in most, but not all, of the treated patients. Also of interest are the variations in the alpha globulins with the various stages of the disease. A third point is the early appearance of the albumin and gamma globulin changes in the primary disease and the stability of these alterations throughout its course in the absence of treatment.

That the alterations in the electrophoretic pattern of syphilitic sera are not diagnostic and cannot be used to differentiate true syphilitic sera from so-called biologic false-positive sera has recently been shown.[2] The present observations support this. In addition the fact that many other diseases produce similar pattern alterations[6,8,15] further diminishes the diagnostic importance of the changes observed in syphilis.

More important, however, than the mere recording of electrophoretic pattern alterations in disease is an attempt to interpret these changes in terms of the physiologic and biochemical significance in the organism. Such an interpretation depends upon an understanding of what the Tiselius apparatus measures, and upon some insight into the biologic function of each component measured.

In the first place, is the electrophoretic pattern a true measure of the protein components of the serum? The electrophoresis apparatus with the modern optical devices[10,12] measures variations in the refractive index of the solution in various parts of the cell after separation of the colloidal components under the influence of an electric field. Calculations of the concentrations of the serum components have been based upon two assumptions: (1) that protein alone influences the refractivity of the dialysed serum, other substances such as lipoid having no appreciable effect and (2) that all serum protein fractions have the same specific refractivity.

Recent work, however, casts some doubt upon the validity of these assumptions. It has been shown that in conditions in which serum lipoids are markedly elevated there is considerable difference between total protein values derived from the refractometric measurement in the electrophoresis apparatus and from nitrogen determination.[19] Some fractions vary in this respect more than others. Thus the albumin fraction is not affected by the high plasma lipid levels and the gamma globulin is little affected, but there is a marked apparent elevation of alpha and beta globulins.

Chief alterations in syphilitic patterns are in those fractions which are little, if at all, altered by serum lipoid. This, coupled with the observation that the serum lipoids are only slightly changed in syphilis,[14] indicates that the pattern changes seen in untreated syphilis probably represent actual changes in protein concentration.

With regard to the biologic significance of alterations in the quantity of the components our knowledge is still meager. Assuming that the present concept of albumin production in the liver[13] is correct, then the lowered level of the serum albumin may indicate some disturbance in this function of the liver in syphilis.

The gamma globulin fraction has been found to contain many of the known antibodies.[5] Whether or not all of the fraction is composed of immune-body globulin is still an unsettled question.[1] A rise in gamma globulin occurs experimentally in animals following the stimulation of antibody production by a wide variety of antigens.[17,18] Many infections or presumably infectious

diseases also produce elevations of gamma globulin.[6,7,8,15] In the case of syphilis the rise in the gamma globulin is not accounted for by the "reagin" since specific absorption of this substance does not significantly alter the magnitude of the gamma peak.[2] It is possible that at least part of the increase in gamma globulin found in the syphilitic sera is in the nature of an anamnestic response and is therefore non-specific. It is evident that as yet we can arrive at no definitive conclusion concerning the significance of this elevation of gamma globulin which occurs not only in syphilis but in so many other diseases as well.

SUMMARY AND CONCLUSIONS

Using the Tiselius method of electrophoresis, studies were made on the proteins of twelve normal, thirty-two syphilitic and three biologic false-positive blood sera. The following conclusions appear warranted: (1) The serum proteins from patients with untreated primary, secondary and tertiary syphilis deviate significantly from normal. Albumin concentration is decreased and gamma globulin concentration is increased in all stages of the disease. Beta globulin is not altered. The alpha-1 globulin is significantly increased in secondary syphilis; the alpha-2 globulin is increased in secondary and tertiary syphilis. (2) Serum patterns of treated secondary and tertiary syphilitics have returned on the average to within normal limits. (3) There is a little if any correlation between positive and negative serologic reactions in syphilis and the presence or absence of electrophoretic pattern alterations. (4) The electrophoretic patterns of three patients with biologic false-positive sera exhibited changes resembling, in part, the changes found in untreated syphilitics, principally a decrease in the albumin concentration.

The possible significance of albumin and gamma globulin alterations in syphilis is discussed.

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Penicillin-resistant Non-hemolytic Streptococcal Subacute Bacterial Endocarditis*

WILLIAM H. CLARK, M.D., SERGIUS BRYNER, M.D. *and* LOWELL A. RANTZ, M.D.
San Francisco, California

THE first reports of the results of penicillin therapy in non-hemolytic streptococcal subacute bacterial endocarditis were not spectacular and many relapses occurred. However, only small amounts of the drug had been employed. Subsequently, with higher dosages, more and more patients have been cured, including many with "resistant" strains of streptococci. The value of supplementing penicillin therapy with anticoagulants, sulfonamides, streptomycin and renal tubular blocking substances has been considered. Various technics for the administration of penicillin have been advocated and the duration of treatment has varied widely among different investigators.

The one point of agreement has been the realization that large daily doses of penicillin should be used in every case of this disease. Failure to control the infection with one dosage schedule requires a substantial increase in the amount of drug. Perseverance and the administration of very large to truly massive doses of penicillin have frequently resulted in the ultimate cure of patients who had suffered repeated relapses. The large supplies of highly refined penicillin now available permit the use of quantities sufficient for the cure of nearly every case of subacute bacterial endocarditis.

The purpose of this paper is to present nine cases of subacute bacterial endocarditis, treated in the Stanford University Hospitals, which have required the administration of 1 to 12 million units of penicillin daily. A resumé of the experience of other investigators with resistant endocarditis precedes the case reports. Brief comments concerning the individual problems encountered follow each summary, and a discussion of some of the general considerations involved in the treatment of bacterial endocarditis is presented in conclusion. No consideration will be given to factors such as pathogenesis, etiology, diagnosis or complications.

REVIEW OF THE LITERATURE

The need for administration of a million or more units of penicillin per day in the management of some of the more stubborn cases of subacute bacterial endocarditis has already been stressed by numerous investigators. Several of these studies will be mentioned to emphasize the importance of more energetic treatment after failure has repeatedly followed therapy with smaller doses of penicillin.

Dawson and Hunter[1,2] eradicated the infection in twenty successive cases after supplies of penicillin became adequate. Failures occurred in a few of the fifteen previously treated patients. In four cases at least one course of a million or more units of penicillin per day was required. One patient, Case 16, after a total of 103 days of treatment with 200,000 to 500,000 units daily had failed, also relapsed following a period of twenty-eight days during which he received 1,000,000 units daily. Arrest of the infection was finally effected when 2,000,000 units were given daily for two weeks. Another patient, Case 17, was similarly cured when given 1,000,000 units for twelve days subsequent to 106 days of

* From the Department of Medicine, Stanford University School of Medicine, San Francisco, Calif.

ineffective treatment with dosages as great as 500,000 units daily. In Case 25 the daily administration of 1,000,000 units for two weeks saw successful whereas relapse had followed treatment with 500,000 units daily for twenty days.

A different problem was encountered with Case 32. Relapse occurred after a course of treatment consisting of 500,000 units for ten days and again after 1,000,000 units had been administered daily for two weeks. A successful result was then achieved by giving 500,000 units for four weeks.

Hunter briefly mentioned four additional cases in a more recent communication.[3] The first received 20,000,000 units of penicillin per day for sixteen days after multiple failures had followed treatment with daily doses of 400,000, 500,000, and 1.5, 2, 5 and 10 million units. The patient died a few weeks later of congestive heart failure, but no signs of active infection could be found at autopsy. Two patients whose infecting organisms required 1.0 unit of penicillin per ml. for inhibition *in vitro* were successfully treated with 5 and 10 million units, respectively, daily for three weeks. The fourth was a case of enterococcal endocarditis in which 8.0 units of penicillin per ml. were needed for *in vitro* inhibition. A combination of 4,000,000 units of penicillin and 4 Gm. of streptomycin given daily for four weeks apparently arrested the disease.

Mokotoff, Brams, Katz and Howell[4] reported that large doses of penicillin were necessary in three of seventeen cases of endocarditis. Relapse and death due to the infection followed the daily administration of 1,000,000 units for fifteen days in one case. This patient had previously received smaller amounts of penicillin for 143 days. The second patient recovered when 1.2 to 3 million units per day were administered for twenty-eight days after smaller amounts of the drug had been ineffective during 117 days of treatment. A less sensitive organism was encountered in the third case. Seven days with 1,000,000 units and fourteen days with 2,000,000 units completed a continuous course of seventy-six days of therapy.

Gerber, Schwartzman and Baehr[5] mentioned a case of enterococcal endocarditis treated with 10,000,000 units of penicillin daily for five weeks. Blood cultures remained sterile while therapy was in progress but relapse occurred one week after its completion.

Avery, Mayer and Nelson[6] successfully treated a patient whose disease was of two years' duration. Inadequate doses of penicillin had been employed irregularly for eighteen months. The causative organism developed moderate resistance and finally required 1.4 units of penicillin per ml. of medium for inhibition. The administration of 3,000,000 units for seventeen days and then of 1,500,000 units with diodrast or para-aminohippuric acid for twenty additional days was effective.

Loewe, Rosenblatt and Alture-Werber[7] recently presented a most unusual case of very resistant endocarditis due to Veillonella gazogenes. *In vitro* inhibition required 30 units of penicillin per ml. of culture medium. The patient received many weeks of treatment during which daily amounts of 500,000 to 10,000,000 units of penicillin, with and without concomitant sulfonamide therapy, were tried. A total of 466,000,000 units was administered. Then when 240 Gm. of sodium para-aminohippurate were given with 10,000,000 units of penicillin daily for sixteen days, the disease was clinically arrested.

Priest, Smith and McGee[8] stated that their last fifteen patients have all recovered and that most of these have received at least 1,000,000 units of penicillin per day.

Morgan[9] treated a very stubborn case of endocarditis of undetermined etiology with 20,000,000 units of penicillin for twenty days. The patient died of congestive heart failure one month after treatment was started. At autopsy the lesions of bacterial endocarditis were scarred and apparently healed.

PRESENTATION OF CASES

Selection of Cases. Thirty-three patients with subacute bacterial endocarditis have been treated on the medical service of the

Stanford University Hospitals since 1943. The first twenty-one patients, because of the scarcity of penicillin, were selected for treatment only if the causative organism required not more than 0.1 unit of penicillin per ml. of culture medium for *in vitro* inhibition. These cases have been analyzed in previous reports by Bloomfield, Armstrong and Kirby,[10] and by Bloomfield and Halpern.[11] Case I of the series to be presented is the last of that selected group and has previously been reported as Case 4 in the paper by Bloomfield and Halpern. Cases II through VIII are all among the last twelve consecutive and unselected cases to be treated on the medical service. Case IX has been under the care of the Department of Pediatrics and permission to include it in this group has been kindly granted by Dr. H. K. Faber.

Details of the physical and laboratory examinations, such as the presence of petechiae, splenomegaly, leukocytosis, anemia and electrocardiographic abnormalities, have been omitted from the summaries. The essential data of treatment and bacteriologic studies have been tabulated.

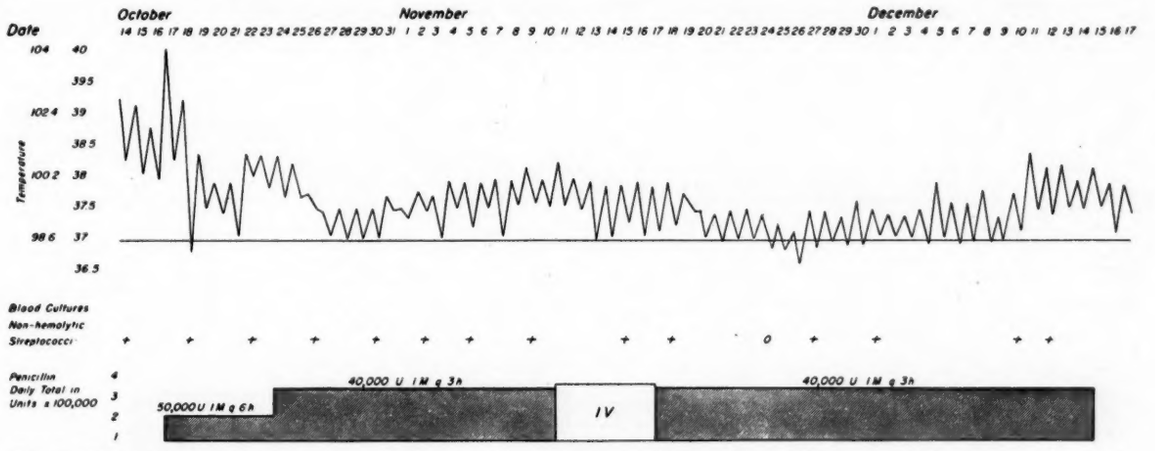

FIG. 1. Case I, first ineffective course of therapy. Note that penicillin sensitivity data were not incorporated in this graph. There was inhibition initially by 0.1 to 0.2 unit of penicillin per ml. of medium.

CASE REPORTS

CASE I. N. G., a forty-eight year old female, entered this hospital on October 14, 1944, with a febrile illness of six weeks' duration. Several blood cultures were positive for non-hemolytic streptococci, and the diagnosis of subacute bacterial endocarditis probably superimposed on a congenital septal defect was made. *In vitro* sensitivity studies revealed inhibition of the organism to be partial with 0.1 and complete with 0.2 unit of penicillin per ml. of medium.

The details of therapy and the course during the first sixty days of ineffective treatment are shown in Figure 1 and Table I. The patient was readmitted on January 3, 1945, after three weeks at home. Combined therapy with penicillin and sulfadiazine was unsuccessful. Definite increase in the resistance of the organism to penicillin occurred during this phase. (Fig. 2.) A successful outcome followed the use of 1,000,000 units of penicillin per day for sixty days. (Fig. 3.) She has remained free from any evidence of active infection for over eighteen months.

Comment. This case is reported for the second time as it illustrates the principal contribution of this paper, namely, that subacute bacterial endocarditis can be cured by the use of larger amounts of penicillin after many weeks of treatment have been ineffective.

The increase in the resistance of the causative organism from 0.2 to 1.0 unit of penicillin per ml. of culture medium during the period when subcurative amounts of the drug were being given should be noted.

Experience with subsequent cases indicates that initial treatment should have been with 1,000,000 units of penicillin daily as the organism was only moderately sensitive according to *in vitro* measurements.

CASE II. F. S., a sixty-nine year old male, was first seen in this clinic on August 28, 1945, with a febrile illness of four months' duration. The presence of subacute bacterial endocarditis had been suspected at another hospital but no positive blood cultures were obtained. A total of 1,700,000 units of penicillin had been given in irregular doses between July 12 and August 7, 1945. The diagnosis was verified by the recovery of non-hemolytic streptococci from the blood. Sensitivity studies revealed complete inhibition by 0.2 unit of penicillin per ml. of medium. Aortic stenosis, presumably rheumatic in origin, was the underlying valvular lesion.

Therapy is outlined in the table. Interest in the efficacy of a single daily injection of a large dose of penicillin resulted in the schedule used between August 31st and October 6th. The administration of 1,000,000 units for four days was due to a misunderstanding regarding the re-evaluation of the sensitivity studies. Cultures were sterile during the first thirty-seven days of this regimen. When they again became positive, therapy was changed to a smaller daily amount of penicillin but given in seven divided doses. This was continued for twenty-three days during which time blood cultures were sterile. Relapse occurred three weeks later, after the patient had been dismissed. The *in vitro* sensitivity of the newly isolated organism was 0.1 unit per ml.

Sixty days' treatment with 1,000,000 units of penicillin daily was successful in producing clinical arrest of the disease. There have been no signs of infection for twelve months since his discharge. Moderate congestive heart failure has developed but it is well controlled with digitalis and restriction of activity.

Comment. This case is not as important in regard to the purpose of this paper as the others because relapse followed inadequate therapy. The only conclusion possible regarding the single daily injection of penicillin is that, with the dose employed, there was failure. The organism required 0.2 unit of penicillin per ml. for *in vitro* inhibition. In accordance with current concepts, 1,000,000 units of the antibiotic should have been administered daily when therapy was first instituted.

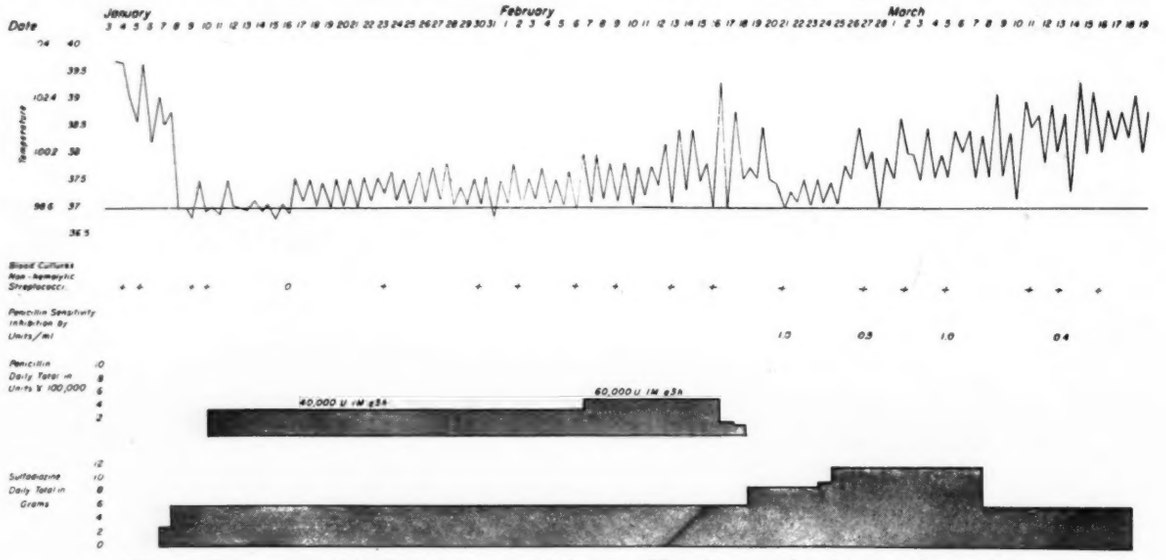

FIG. 2. Case I, second ineffective course of therapy. Note increased resistance of organism.

CASE III. J. K., a thirty-nine year old male, was first seen in this clinic on October 30, 1945, with an illness of eighteen months' duration. Severe scarlet fever in March, 1944, was followed by six months of poor general health. The diagnosis of subacute bacterial endocarditis was made in September, 1944, when persistent daily fever developed, several blood cultures contained non-hemolytic streptococci and a heart murmur was noted for the first time. Penicillin was administered for more than eight weeks (Table I) following which the patient remained quite well for three months. An attack of acute tonsillitis occurred on February 28, 1945, and the first positive blood culture in over five months was obtained ten days later. Treatment was irregular during the next ninety

days and then was allowed to lapse for four months prior to entry to this hospital.

The diagnosis of subacute bacterial endocarditis was confirmed by the recovery of nonhemolytic streptococci from several blood cultures. The penicillin concentration required for *in vitro* inhibition was 0.4 unit per ml. The valvular lesion was that of aortic insufficiency, presumably on a rheumatic basis.

Bacterial arrest followed treatment with 1,000,000 units of penicillin for sixty days. (Table 1.) No evidence of infection has been demonstrated in the subsequent year.

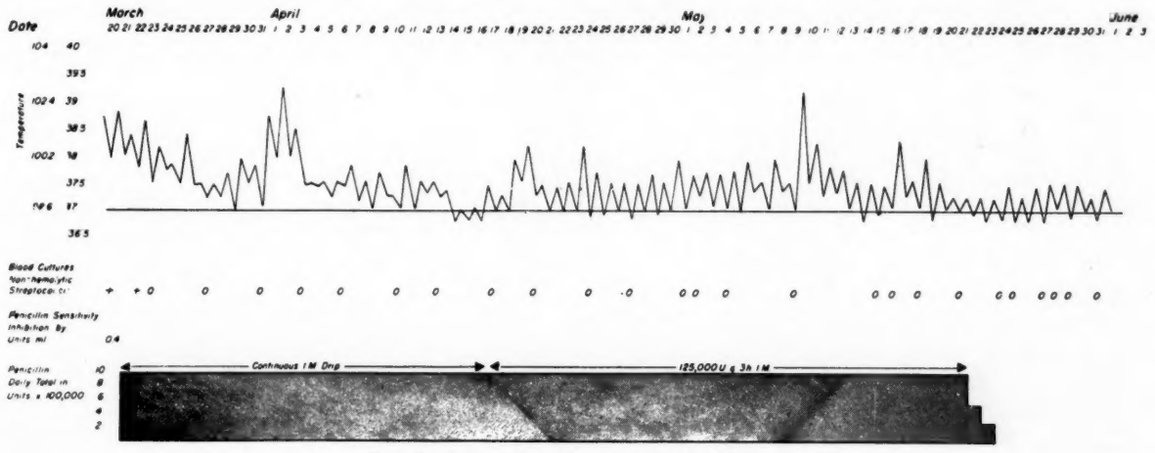

FIG. 3. Case 1, curative course of therapy.

Comment. Several interesting aspects of this case deserve consideration. The prolonged illness started with an attack of scarlet fever eighteen months before admission to this clinic. This acute episode was followed by six months of generally poor health. Bacterial endocarditis may have been present during this time but it seems more probable that it was a period of active rheumatic heart disease.

A definite diagnosis of subacute bacterial endocarditis was established in September, 1944, and penicillin was given for two months. No streptococci were recovered from blood cultures until after an episode of acute pharyngitis three months later. This may actually have been an instance of reinfection rather than relapse.

One million units of penicillin per day were employed because the causative organism required 0.4 unit of penicillin per ml.

CASE IV. G. S., a thirty-nine year old male, was first seen in this clinic on March 6, 1946, with subacute bacterial endocarditis of four months' duration. Treatment at another hospital (Table 1) had been completely unsuccessful as positive blood cultures had been obtained while therapy was still in progress. Nonhemolytic streptococci were recovered from blood cultures on three occasions prior to instituting treatment at this clinic. The *in vitro* requirement for inhibition was 0.2 unit of penicillin per ml. of medium. A congenital septal defect was the most probable anatomic cardiac lesion. Nine months after the conclusion of sixty days' treatment with 1,000,000 units daily (Table 1), there was no evidence of active infection nor of congestive heart failure.

Comment. One million units of penicillin daily were used in the treatment of this case because satisfactory results had not been obtained during ten weeks of therapy with 200,000 and 300,000 units daily. In addition the causative organism was slightly resistant to the action of penicillin as 0.2 unit per ml. was required for complete *in vitro* inhibition.

CASE V. This case is presented in more detail because of its extreme complexity. C. R., a forty-three year old male, was first seen in this clinic on March 15, 1946. There had been sudden onset of weakness and fever about a

month prior to entry and he had received 1,900,000 units of penicillin in small and irregular doses during the next thirty days. Nonhemolytic streptococci recovered from blood cultures at this hospital required 0.4 unit of penicillin per ml. of medium for complete *in* preparation to a less refined product and anorexia, lassitude, nausea, vomiting, severe dizziness, fever and marked discomfort at the sites of injection developed within twenty-four hours. These symptoms became steadily worse and the use of the drug was discontinued.

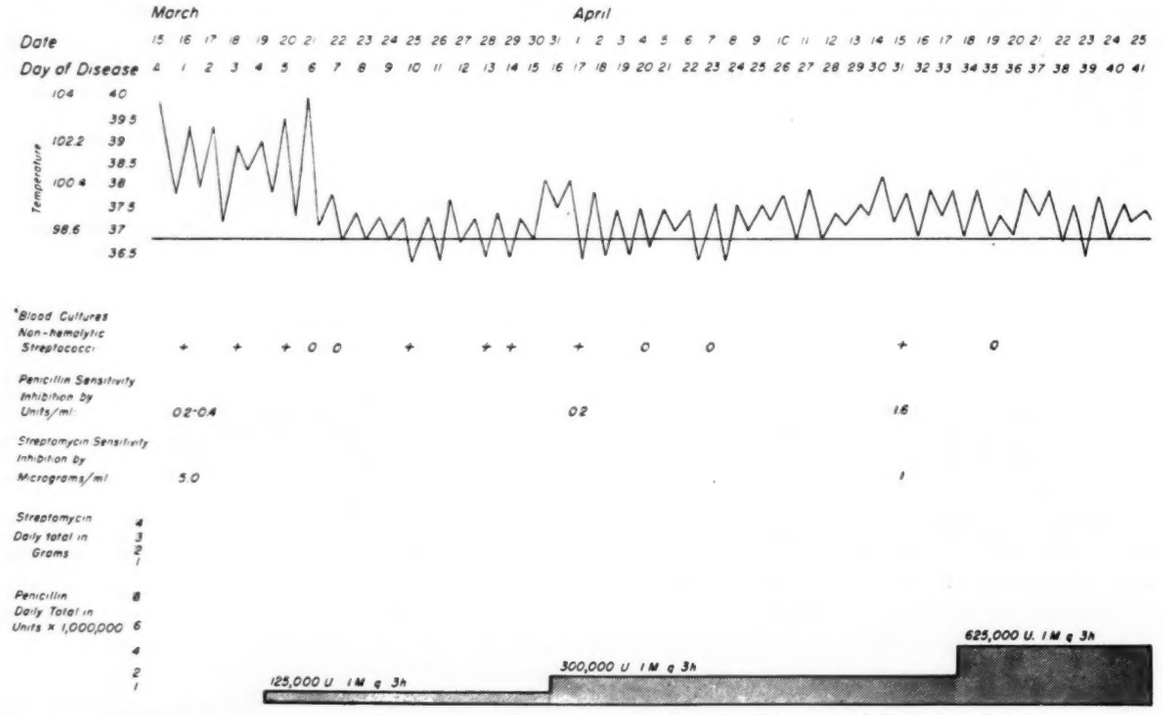

FIG. 4. Case v, initial ineffective penicillin therapy with 1,000,000 to 5,000,000 units daily.

vitro inhibition. A systolic murmur, the presence of which had been known to the patient for twenty years, was heard and some observers also detected a diastolic murmur of mitral stenosis.

The various penicillin and streptomycin dosage schedules employed and their effect on the temperature, blood cultures and sensitivity of the causative organism are given in Table 1 and in Figures 4, 5 and 6.

The patient's general condition improved greatly during the first phases of therapy with 1 to 5 million units of penicillin daily, but blood cultures were not consistently negative. The alarming increase in the resistance of the organism to penicillin and the fact that 5 micrograms of streptomycin per ml. of culture medium produced complete inhibition suggested the use of the latter agent.

There were no toxic effects resulting from the daily administration of 4 Gm. of the drug, other than mild tinnitus for fifteen days. It was then necessary to change from a highly purified

Penicillin was administered temporarily while a new supply of purified streptomycin was being obtained. Streptomycin was then employed again and no untoward reactions occurred until a different preparation was substituted seven days later. All toxic symptoms reappeared within thirty-six hours and the drug was withdrawn.

There was no antibiotic therapy during the next three weeks. The main toxic symptoms resulting from the administration of streptomycin disappeared although there was slight residual vertigo. Daily fever was present and blood cultures were positive. *In vitro* studies revealed an increase in sensitivity to penicillin, to that originally obtained. Moderate resistance to streptomycin had developed.

All toxic reactions had occurred when less highly refined preparations of streptomycin were employed and for that reason a third trial with the purified drug was made when a new supply was available. Toxic symptoms were very severe almost immediately. In addition to the effects previously mentioned, there was marked

numbness and tingling around the mouth and along the distribution of the left ulnar nerve. The use of the drug was promptly discontinued.

Bacterial arrest of the disease was finally achieved following sixty days of treatment with 8,000,000 units of crystalline penicillin daily.

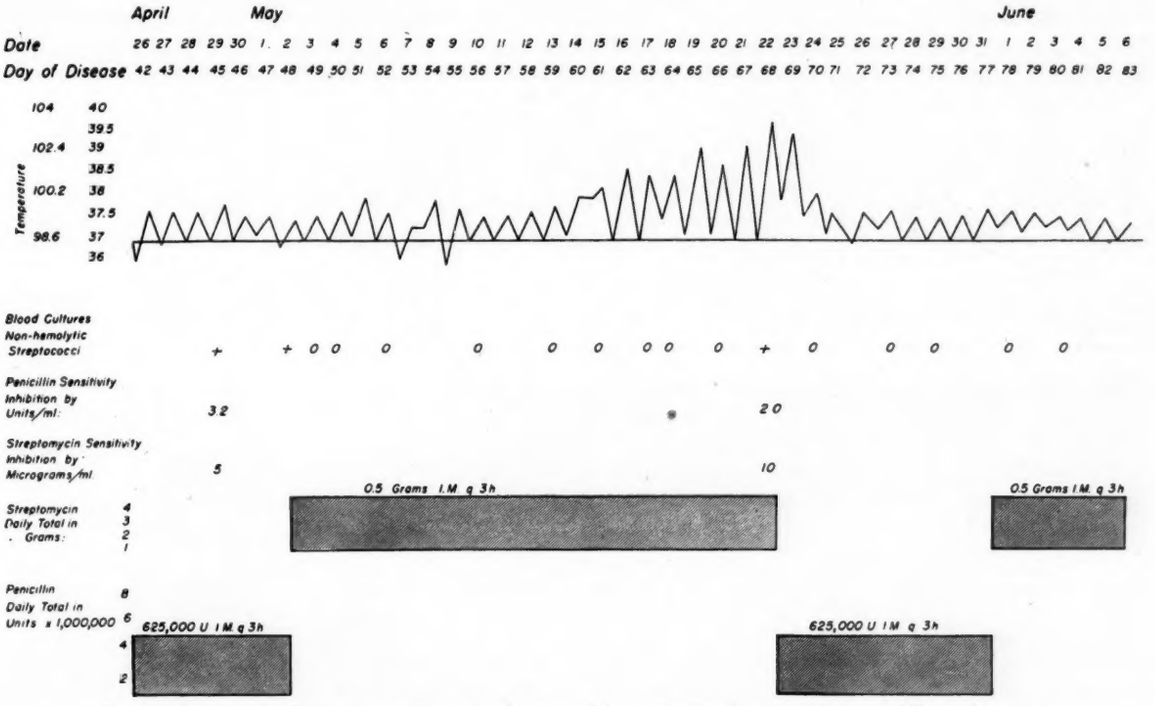

FIG. 5. Case v, ineffective streptomycin therapy. Note extreme increase in penicillin resistance.

(Fig. 6.) Sample serum penicillin levels 30, 60 and 120 minutes after an intramuscular injection of 1,000,000 units of penicillin were 10, 6.7 and 4 units per ml., respectively. These figures represent levels fifty-fold to ten-fold greater than the *in vitro* inhibiting concentration of 0.2 to 0.4 unit per ml. of medium.

This patient received 627,000,000 units of penicillin and 121.5 Gm. of streptomycin during 175 days in the hospital.* During the follow-up period of five months since discharge there has been no evidence of active infection. Minimal signs of congestive heart failure have recently been noted.

Comment. This case, without doubt, can be considered a real medical triumph. It illustrates the desirability, even obligation, of performing *in vitro* sensitivity studies before instituting treatment and frequently thereafter in cases not promptly rendered bacteria-free. The first clue suggesting that this might be a resistant case was the initial sensitivity figure of 0.2 to 0.4 unit of penicillin per ml. of medium required for inhibition. Had that information not been at hand, 1,000,000 units per day would not have constituted the starting dose and more time would have been lost with even less effective treatment. Subsequently, repeated sensitivity studies revealed a steady increase in the resistance of the organism to 1.6 and 3.2 units per ml. while 2.4 and 5 million unit daily doses failed to control the infection. Valuable information was also gained from the streptomycin sensitivity studies.

The practical aspects of giving 1,000,000 units of penicillin in a single dose intramuscularly, as when the patient was receiving 8,000,000 units daily, are important. It was necessary to use crystalline penicillin. Very little discomfort was experienced by the patient when the full amount was confined to a volume of 6 ml., of which 1 ml.

* The Commercial Solvents Corporation generously supplied large amounts of crystalline penicillin for the treatment of this patient. The streptomycin used was allocated by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

was 1 per cent procaine solution. The muscles of the thighs were utilized as well as those of the buttocks and the sites of injection were carefully rotated.

The value of giving a "rest" from penicillin administration in cases in which there is a marked increase in the resistance of the organism to the drug during treatment is clearly demonstrated. During a five-week period when no penicillin was administered the causative organism reverted from the high degree of acquired resistance to the original degree of moderate sensitivity. It is of interest that resistance to streptomycin was increasing meanwhile during the administration of that agent. The most important of all lessons learned from this difficult case, however, was that of the need for perseverance in spite of a long period of failure.

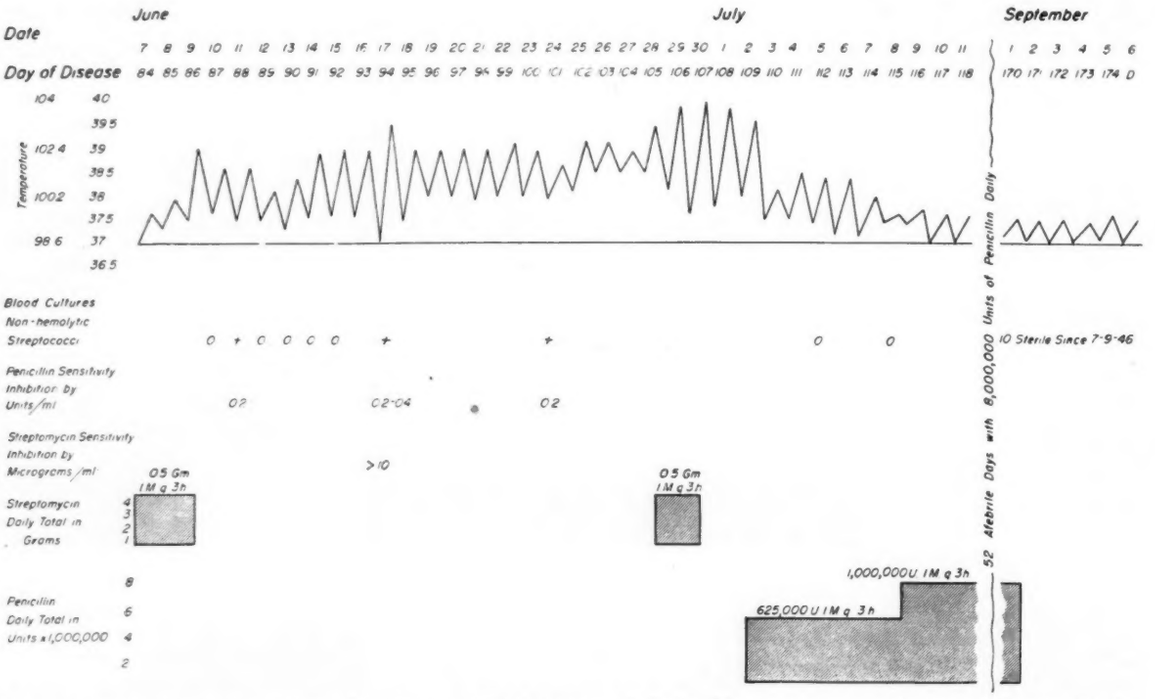

FIG. 6. Case V, curative penicillin therapy with 8,000,000 units daily. Note return to initial penicillin sensitivity.

CASE VI. J. W., a forty-five year old male, entered this hospital on April 2, 1946, with a febrile illness of six to eight months' duration. A presumptive diagnosis of subacute bacterial endocarditis had been made elsewhere without bacteriologic confirmation in January, 1946, and penicillin had been administered fairly regularly for sixty days during which time roughly 10,000,000 units had been given in intermittent intramuscular injections. Daily dosages of 400,000 units had been employed during the last three weeks. Failure was indicated by the persistence of fever and general symptoms.

Non-hemolytic streptococci were recovered from the blood at this clinic. The organism required 0.4 unit of penicillin per ml. of medium for complete inhibition. A diagnosis was made of subacute bacterial endocarditis on the basis of inactive rheumatic heart disease. Therapy is indicated in Table I.

The evaluation of progress was complicated by the presence of moderate fever almost daily during treatment. Much discomfort resulted from the administration of 500,000 units of amorphous penicillin intramuscularly every three hours. This was minimized by diluting the drug in 4.0 ml. of distilled water and 1.0 ml. of 1 per cent procaine solution. Half of this was given in each thigh or buttock. Several areas of subcutaneous aseptic necrosis developed. All blood cultures taken during treatment and during the eight months' follow-up period have been sterile. The fever promptly disappeared after the administration of penicillin was discontinued. There has been no evidence of congestive heart failure.

Comment. This is a case with a moderately resistant organism. Difficulties had already been encountered in the management of Case v, who was on the ward at the same time, and the penicillin sensitivity figures were initially the same for both cases. These influencing facts resulted in the use of 4,000,000 units of penicillin daily.

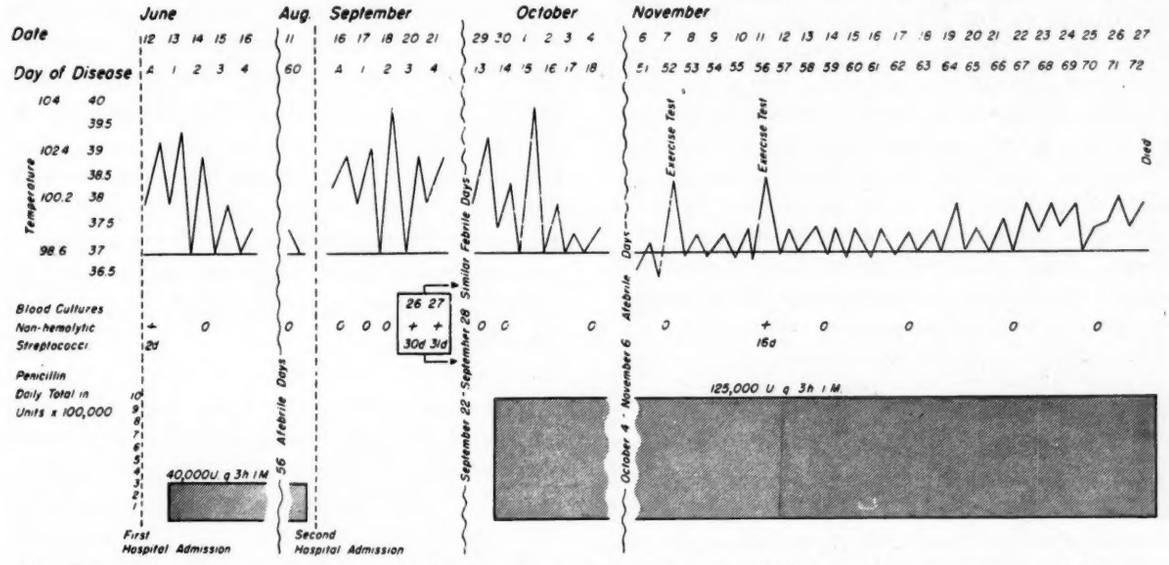

FIG. 7. Case VII, failure to eradicate infection in subacute bacterial endocarditis caused by streptococcus which was inhibited *in vitro* by 0.05 unit of penicillin. Note that sixteen to thirty-one days were required for growth of the organism in blood cultures after relapse.

This case illustrates what others have noted, namely, that occurrence of fever during treatment, if the blood cultures are sterile, does not necessarily indicate inadequate therapy. In this instance the continued fever was probably due to the local tissue reactions resulting from the administration of large amounts of amorphous penicillin. These reactions were more severe than those experienced by other patients receiving much larger doses of crystalline penicillin (Cases v and VIII).

CASE VII. F. T., a forty-one year old male, entered this hospital on June 12, 1946, with a febrile illness of five months' duration. The patient had known that he had rheumatic heart disease. A tooth was extracted in October, 1945. The onset of fever and beginning weight loss was in January, 1946. Several blood cultures, taken in another hospital in April, were sterile.

Non-hemolytic streptococci were isolated from blood cultures at this clinic on June 8th and 12th. Growth occurred in forty-eight hours and *in vitro* sensitivity studies revealed complete inhibition of the organism by 0.05 unit of penicillin per ml. of medium.

Marked aortic insufficiency was indicated on entry by the blood pressure, which was 124/30, and by the x-ray demonstration of a moderately enlarged heart. There were no signs of congestive heart failure. Daily dosages of 320,000 units (Table I and Fig. 7) were employed as the causative organism was very sensitive to penicillin. The course during the sixty days of treatment was ideal and the patient was discharged with the disease apparently arrested.

Fever recurred two weeks later and a nonproductive cough developed but blood cultures were negative. Symptoms persisted and the patient was hospitalized on September 16th. Clinically, relapse had occurred but no organisms could be recovered from the circulating blood during two weeks of observation prior to the re-institution of treatment with 1,000,000 units of penicillin per day. (Table I and Fig. 7.) There had been a further increase in the size of the heart but frank congestive heart failure was not present.

Growth appeared in two blood cultures thirty and thirty-one days after they had been taken. The organism was a streptococcus morphologically but it could not be subcultured and sensitivity studies were technically impossible.

Progress during the first month of the second course of treatment seemed entirely satisfactory. Penicillin serum levels were 4.0, 2.0, 0.6, and 0.4 units per ml. 30, 60, 120 and 180 minutes, respectively, after the injection of 125,000 units intramuscularly.

The first bout of nocturnal dyspnea occurred on November 4th. Râles and venous distention were present. Prompt digitalization was effective. On November 7th and November 11th graded exercise tests, using a pedal board, were given as part of a special study. Each test lasted about five minutes. A moderate chill and an abrupt transient elevation in the temperature occurred about thirty minutes after each of these. (Fig. 7.) Blood cultures were obtained during both chills and growth appeared sixteen days later in the one taken on November 11th. The organism was a streptococcus but could not be subcultured. No other blood cultures during the second course of treatment were positive.

Dyspnea became very severe on November 22nd and the patient died of congestive heart failure on November 27, 1946. At autopsy the aortic valve was found to be greatly distorted, with marked fibrosis, fusion of the commissures and shortening and perforation of the leaflets. Fresh vegetations were attached to the torn cusps. An active inflammatory process and many gram-positive cocci were demonstrated by histologic examination. Cultures made from bits of ground vegetation yielded diphtheroids and overgrowth by these contaminating organisms prevented the possible isolation of the slow-growing streptococci.

Comment. This was the only failure in the group. There was a difficult bacteriologic problem. Streptococci were recovered in forty-eight hours from blood cultures taken on entry to this clinic. Growth and subcultures were satisfactory. The original sensitivity figure of 0.05 unit of penicillin per ml. of medium therefore seems perfectly valid. After relapse had occurred no growth was detected in blood cultures until there had been thirty days of incubation. The advisability of keeping all cultures for at least a month before discarding them as sterile is illustrated.

The well known fact that the prognosis must be extremely guarded while treatment is in progress is exemplified by this case. The clinical response was ideal during the entire sixty-day period of initial therapy. The temperature fell quickly to normal and blood cultures were repeatedly sterile.

Penicillin in amounts greater than 1,000,000 units per day should, perhaps, have been used since there were incomplete data about an organism which had resisted earlier treatment. The clinical response during the first month of the second course of penicillin therapy was also very satisfactory and hence misleading. The single positive blood culture obtained during the course of treatment, because of its very slow growth, gave information too late to permit a further increase in the penicillin dosage prior to death.

CASE VIII. C. G., a fifty-four year old male, entered this hospital on June 21, 1946. Fever, weakness and weight loss had been present since May, 1945. The diagnosis of subacute bacterial endocarditis, due to an enterococcus, was made at another hospital in May, 1946. A congenital septal defect was considered to be the underlying abnormality. Treatment with 300,000 and 800,000 units of penicillin daily was given during the four weeks prior to transfer to this hospital.

Non-hemolytic enterococci (Streptococcus faecalis), requiring 10.0 units of penicillin per ml. of culture medium for inhibition, were recovered from the blood. There was evidence of a diffuse renal lesion. The following data were derived from a timed urine examination with Addis count: specific gravity 1.013, total protein excretion 0.3 Gm. per twenty-four hours, 1,000,000 casts per twenty-four hours, 98,000,000 white and epithelial cells, and 44,000,000 red blood cells per twenty-four hours. Phenolsulfonphthalein excretion was 27 per cent in two hours. The blood urea concentration was 66 mg. per 100 ml.

Crystalline penicillin* was used exclusively for treatment, 12,000,000 units per day being administered. (Table 1). The last thirty days of therapy were received at a hospital of the Veterans' Administration. Thirty minutes after an intramuscular injection of 1,500,000 units, serum levels were as high as 100 units per ml.,

* A large quantity of crystalline penicillin was donated by the Commercial Solvents Corporation for the treatment of this patient.

and two hours later, 20 to 50 units per ml. were still present.

An erythematous macular rash developed on two occasions during therapy. This promptly disappeared following the administration of benadryl.

The clinical response was prompt and sustained. There has been no evidence of active infection during the six months since the completion of therapy. The status of the renal lesion, however, remains in doubt. The blood urea has remained slightly elevated, the last determination being 53 mg. per 100 ml. Urinary protein excretion has decreased from 0.3 to 0.09 Gm. per twenty-four hours but the patient's blood pressure has progressively risen from 130/78 to 190/118. There has been no evidence of congestive heart failure.

Comment. The causative organism in this case was an enterococcus (Streptococcus faecalis) requiring 10.0 units of penicillin per ml. for *in vitro* inhibition. Truly massive daily amounts of penicillin must be administered in order to obtain serum concentrations of the drug adequate to affect such an extremely resistant organism. Doses of 8,000,000 and 12,000,000 units per day were employed with success. Due to moderate renal insufficiency, serum penicillin levels were several-fold greater than are usually obtained with comparable doses. It is probable that arrest of the disease might not have been achieved had renal function been normal.

Case IX. R. F., a nine year old schoolboy, entered the pediatric service on October 17, 1946, with a febrile illness of ten days' duration. Non-hemolytic streptococci were recovered from blood cultures. *In vitro* inhibition was complete in a concentration of 0.05 unit of penicillin per ml. of medium. The boy was moderately cyanotic and congenital pulmonic stenosis without other anatomic abnormalities was demonstrated by angiograms.

Treatment with 400,000 units of penicillin daily for fifty-one days (Table 1) was accompanied by prompt clinical response. All blood cultures were sterile. The child was discharged one week after the completion of therapy.

Two blood cultures, taken two and four days, respectively, after the last injection of penicillin were positive nine days later. The slow growing organism was morphologically a streptococcus but it could not be subcultured. No penicillin sensitivity studies were possible.

Moderate fever was present when the child was re-admitted on December 21, 1946. Penicillin therapy was re-instituted and the daily dosage increased to 2,000,000 units. (Table 1.) The duration of treatment was twenty-four days. There was occasional low-grade fever while therapy was in progress but blood cultures were consistently negative. All blood cultures have been sterile for eight weeks following the conclusion of treatment.

Comment. This boy weighed only 23 Kg. so the initial daily dose of 400,000 units of penicillin was very liberal. The organism was highly sensitive to penicillin. Treatment was prolonged and the clinical course ideal but relapse occurred within two days. The cultural characteristics of the streptococcus recovered had changed greatly; growth was slow and subculturing impossible.

The recent experience with Case VII had been very similar and it was of great influence in reaching the decision to increase the daily dose of penicillin five-fold and continue treatment for only three weeks. It is still much too early to know how successful such a regimen may have been. This is another instance in which apparent arrest of the disease during active therapy was very misleading.

COMMENT

Penicillin Dosage. Dosage schedules, as proposed in some of the more encouraging of the earlier reports of penicillin therapy in subacute bacterial endocarditis,[1,10,12,13] were of necessity restricted because small supplies of the drug were available. Only cases with very sensitive causative organisms could be effectively treated. These reports indicated that penicillin in daily doses of 100,000 to 300,000 units was effective in a large percentage of the cases and, until about the middle of 1945, it was believed that 300,000 units comprised an adequate initial daily dosage. Subsequently, numerous patients were cured only when larger amounts of the drug were employed.

TABLE I

Case No.	Patient Sex, Age	Primary Cardiac Disease	Probable Duration of Infection*	Infecting Organism		Penicillin	Penicillin				Duration of Follow-up	Remarks
				Type	Inhibition by Penicillin (units/ml.)	Dates of Therapy	Dose in Units and Route	Total Units Daily	No. of Days	Total per Course and Patient		
I	N. C. F, 48	Congenital? Septal defect?	6 weeks	Non-hemolytic streptococci	0.2	a. 10/17/44–10/24/44	50,000 q 6 h I.M.	200,000	8		20 mo.	Recovered; no cardiac symptoms
						10/25/44–11/8/44	50,000 q 4 h I.M.	300,000	15			
					0.4	11/9/44–11/16/44	400,000 I.V. drip	400,000	7	First 60 days		
						11/17/44–12/16/44	40,000 q 3 h I.M.	320,000	30	18,280,000		
						b. 1/10/45–2/8/45	40,000 q 3 h I.M. + S.D. 6 Gm./d.	320,000	30			
					0.5	2/9/45–2/16/45	60,000 q 3 h I.M. + S.D. 6 Gm./d.	480,000	7			
					1.0					Second 40 days		
					0.5	2/17/45–2/19/45	20,000 q 3 h I.M. + S.D. 9 Gm./d.	160,000	3	13,540,000		
						c. 3/21/45–4/15/45	1,000,000 I.M. drip	1,000,000	26	24,000,000		
						4/18/45–5/18/45	125,000 q 3 h I.M.	1,000,000	34	33,750,000		
									160	89,570,000		
II	F. S. M, 69	Rheumatic, aortic stenosis	4 months	Non-hemolytic streptococci		a. (another hospital) 7/12/45–8/7/45	I.M.—divided doses	100,000 to 125,000	25	1,700,000	12 mo.	Recovered; congestive heart failure; 10 mo. digitalized
					0.2	b. 8/31/45–9/13/45	500,000 I.M.—single dose	500,000	14			
						9/14/45–9/17/45	125,000 q 3 h I.M.	1,000,000	4			
						9/18/45–10/6/45	500,000 I.M.—single dose	500,000	19			
					0.2	10/7/45–10/29/45	30,000 q 3 h I.M. × 7	210,000	23	22,245,000		
					0.1	c. 12/7/45–2/5/46	125,000 q 3 h I.M.	1,000,000	60	60,000,000		
									145	83,945,000		
III	J. K. M, 39	Rheumatic, aortic insufficiency	18 months	Non-hemolytic streptococci		a. (another hospital) 9/26/44–12/8/44	I.M.—divided doses	120,000–200,000	74	9,210,000	13 mo.	Recovered; no cardiac symptoms
						3/20/45–7/2/45 (Irregular)	I.M.—divided doses	240,000–300,000	103	?		
					0.4	b. 11/13/45–1/13/46	125,000 q 3 h I.M.	1,000,000	60	60,000,000		
									237	69,210,000+?		
IV	G. S. M, 39	Congenital? Septal defect	4 months	Non-hemolytic streptococci		a. (another hospital) 12/11/45–1/18/46						
						1/19/46–2/19/46	50,000 q 6 h I.M.	200,000	39	7,800,000	9 mo.	Recovered; no cardiac symptoms
					0.2	b. 3/9/46–5/8/46	50,000 q 4 h I.M.	300,000	32	9,600,000		
							125,000 q 3 h I.M.	1,000,000	60	60,000,000		
									132	77,400,000		

TABLE I—(*Continued*)

Case No.	Patient Sex, Age	Primary Cardiac Disease	Probable Duration of Infection*	Infecting Organism		Penicillin	Penicillin				Duration of Follow-up	Remarks
				Type	Inhibition by Penicillin (units/ml.)	Dates of Therapy	Dose in Units and Route	Total Units Daily	No. of Days	Total per Course and Patient		
V	C. R. M, 43	Rheumatic? Mitral	1 month	Non-hemolytic streptococci	0.2–0.4 1.6 3.2 SM[1]-5 mμ 2.0 SM[1]-5 mμ–10 mμ 0.2–0.4 SM[1] > 10 mμ	a. 3/20/46–3/31/46 4/1/46–4/17/46 4/18/46–5/1/46 b. 5/2/46–5/22/46 SM 5/22/46–5/30/46 6/1/46–6/8/46 SM 6/9/46–6/27/46 6/28/46–7/1/46 SM c. 7/2/46–7/8/46 7/9/46–9/1/46	125,000 q 3 h I.M. 300,000 q 3 h I.M. 625,000 q 3 h I.M. 0.5 Gm. q 3 h I.M. 625,000 q 3 h I.M. 0.5 Gm. q 3 h I.M. No treatment 0.5 Gm. q 3 h I.M. 625,000 q 3 h I.M. 1,000,000 q 3 h I.M.	1,000,000 2,400,000 5,000,000 4.0 Gm. 5,000,000 4.0 Gm. 4.0 Gm. 5,000,000 8,000,000	12 17 14 21 9 8 3 7 54	11,625,000 40,800,000 70,000,000 81.5 Gm. 45,000,000 32.5 Gm. 7.5 Gm. 35,000,000 425,000,000	5 mo.	Recovered; minimal congestive heart failure
									145	627,425,000 — SM — 121.5 Gm.		
VI	F. T. M. 41	Rheumatic, aortic and mitral	5 months	Non-hemolytic streptococci	0.05 (see text)	a. 6/12/46–8/11/46 b. 10/1/46–11/27/46	40,000 q 3 h I.M. 125,000 q 3 h I.M.	320,000 1,000,000	60 58	19,200,000 58,000,000	Died, congestive heart failure	Cocci in vegetations at autopsy
									118	77,200,000		
VII	J. W. M, 45	Rheumatic type?	9 months	Non-hemolytic streptococci	0.4	a. (another hospital) Feb.–Mar., 1946 b. 4/2/46–4/6/46 4/7/46–4/10/46 4/11/46–5/27/46	Divided doses 40,000 q 3 h I.M. 125,000 q 3 h I.M. 500,000 q 3 h I.M.	200,000 to 400,000 320,000 1,000,000 4,000,000	60 5 4 47	10,000,000+ 1,600,000 4,000,000 183,120,000	8 mo.	Recovered; no cardiac symptoms
									116	198,720,000+		
VIII	C. G. M, 54	Congenital septal defect	13 months	Enterococcus (Streptococcus faecalis)	10.0	a. (another hospital) May–June, 1946 I.M.—divided doses b. 6/22/46–7/1/46 7/2/46–8/21/46	I.M.—divided doses I.M.—divided doses 1,000,000 q 3 h I.M. 1,500,000 q 3 h I.M.	300,000 800,000 8,000,000 12,000,000	21 7 10 50	6,300,000 5,600,000 80,000,000 600,000,000	6 mo. bacteria free	Recovered, increasing hypertension with mild renal insufficiency
									88	691,900,000		
IX	R. F. M, 9	Congenital pulmonic stenosis	10 days	Non-hemolytic streptococci	0.05 (see text)	a. 10/18/46–12/7/46 b. 12/23/46–12/24/46 12/25/46–1/15/47	50,000 q 3 h I.M. 125,000 q 3 h I.M. 250,000 q 3 h I.M.	400,000 1,000,000 2,000,000	51 2 22	19,800,000 1,500,000 42,150,000	2 mo. bacteria free	Recovered
									75	63,450,000		

* When seen in this clinic.
1—Streptomycin sensitivity—micrograms per ml. of medium.
SM—Streptomycin.
S.D.—Sulfadiazine.
I.V.—Intravenous.
I.M.—Intramuscular.

Until recently insufficient data had been accumulated to permit any correlation between studies of the *in vitro* penicillin sensitivity of the causative organism and the response to therapy. It is now known that such tests, at best, are not always reliable guides to treatment but they usually provide valuable information. The technics employed vary in different laboratories. Caution must be exercised when evaluating the results of such studies done by workers inexperienced in these procedures.

There is, nevertheless, fairly general agreement that organisms which are inhibited by 0.1 unit or less of penicillin per ml. of culture medium may be considered sensitive. Those requiring 0.2 to 0.4 unit per ml. are classified as moderately sensitive, and those requiring 0.5 to 5, 10 or more units as moderately to very resistant. Fortunately, about 90 per cent of all nonhemolytic streptococci (Streptococcus viridans is included in this group) fall into the sensitive group.[14] The enterococcus (Streptococcus faecalis) is always very resistant. Most investigators believe that serum penicillin levels of four to eight times the concentration required for *in vitro* inhibition of the organism should be obtained for effective treatment. Data have been accumulated by which serum penicillin levels can be crudely estimated in advance for various doses given by different routes.

Initial daily penicillin dosage schedules derived from the *in vitro* sensitivity of the causative organism may be proposed on the basis of information obtained in the treatment of subacute bacterial endocarditis in this and other clinics.[3,5,14,15,16] Patients with sensitive organisms should receive at least 500,000 units of penicillin daily. If 0.2 to 0.4 unit of penicillin per ml. of culture medium is required for inhibition, the administration of 1 to 2 million units per day is advised. Most patients with organisms inhibited by about 1.0 unit per ml. require 5,000,000 units daily.

The necessary dose for the treatment of cases with very resistant organisms is difficult to estimate. The enterococcus (Streptococcus faecalis) is most frequently encountered in this group and occasionally concentrations of 50 to 100 units per ml. are required for *in vitro* inhibition. It is doubtful whether patients with such excessively resistant organisms can be cured with any practicable amounts of penicillin. Fortunately, most enterococci are inhibited by 5 to 10 units per ml. and the administration of 10 to 20 million units of penicillin per day may well be followed by a satisfactory result. No published reports of the daily use of more than 20,000,000 units of penicillin have appeared, but there is no reason to believe that larger amounts cannot be given if warranted by the clinical situation.

Therapeutic failures in patients with subacute bacterial endocarditis treated with dosage schedules derived from *in vitro* penicillin sensitivity values will continue to occur from time to time. These will be less frequent, however, when there is a rational guide to the initial management, especially when it has been found that the organism is not highly sensitive. Difficulties in treatment can then be anticipated and therapy scaled upward as indicated. All of the cases reported in this paper, except VII and IX, are examples of the usefulness of such knowledge. The exceptions illustrate how *in vitro* tests may be misleading. The causative organisms were apparently most sensitive but treatment was unsuccessful. These failures further emphasize the advisability of using 500,000 or more units of penicillin daily for all patients even though many can be cured with smaller amounts.

It is difficult to estimate the dosage of penicillin which is required when the circulating blood is not sterilized promptly or in patients who have relapsed. The *in vitro* sensitivity of the organism may help in arriving at a decision. Occasionally a definite increase in resistance has occurred. More prolonged treatment with the same inadequate daily dose is not often effective. Drastic increases of five- to ten-fold are advised for every case failing to respond to therapy. Some patients will be overtreated

but this is necessary if the maximal number of recoveries is to be obtained.

Organisms are occasionally encountered which are slow growing and difficult to subculture. Sensitivity studies are then technically impossible. This problem was encountered in Cases VII and IX after relapse had occurred. Whenever bacteriologic information is incomplete, very large amounts of penicillin should be given.

Mention should be made at this point of the identification by Loewe, Plummer, Niven and Sherman[17] of a newly recognized strain of non-hemolytic streptococcus, tentatively called Streptococcus s.b.e. Loewe and Alture-Werber have described cases of subacute bacterial endocarditis due to this strain.[18] Apparently the organism is sensitive to the *in vitro* action of penicillin but is resistant to treatment. The organisms recovered from the nine cases reported have been studied from the standpoint of the cultural and biochemical characteristics described for this strain of streptococcus. None could be fitted into this classification.

Route of Administration. There is disagreement in regard to the route of choice for the administration of penicillin. The advantages of continuous intravenous or intramuscular infusion as compared to intermittent intramuscular injections have been widely discussed. Fairly constant serum levels are maintained at all times during the continuous administration of penicillin; their magnitude depends on the total daily dose. Much higher serum levels, on the other hand, are obtained for thirty to sixty minutes after each single injection when the same daily amount of penicillin is given in multiple divided doses. The more effective route cannot be determined at present as not enough is known about the fundamental mechanism of the action of penicillin on bacteria in the body.

An attractive hypothesis is strongly emphasized by Gerber, Schwartzman and Baehr[5] who believe that the very high (as great as 500 times the *in vitro* inhibiting concentration in the case of very sensitive organisms) serum penicillin levels obtained by giving a "booster dose" twenty minutes after a regularly scheduled injection allow better penetration of the drug into the depths of the vegetations.

There are fewer technical difficulties for the attendants, and the patients are afforded a much greater degree of freedom when the intermittent injection method is used. The criticism that large single doses are poorly tolerated by the patient has been largely overcome by the use of crystalline penicillin. In Case VIII the patient received 1,500,000 units in each injection. Procaine was added to the solution and there was very little local discomfort.

The suggestion has been made[3] that the more simple intermittent intramuscular injection method be used initially in the treatment of subacute bacterial endocarditis but that continuous drip therapy should be employed if results are not satisfactory. All of the patients included in this paper except Case I were treated solely with multiple injections of penicillin.

An additional observation indicates that a twenty-four-hour effective serum penicillin level is not necessary. Although failure occurred when the patient in Case II was treated with a single injection of 500,000 units daily, another patient was clinically cured when 200,000 units were given twice a day for eight weeks. The course was as satisfactory in every way as that of others treated with a similar amount of penicillin in eight smaller doses daily.

It is probable that the route of administration is not important. Good results with all methods have been obtained by satisfying the fundamental requirement that enough penicillin be given during each twenty-four-hour period.

Geiger and Goerner[19] recently presented an encouraging preliminary report on the use of penicillin in oil and beeswax in the treatment of three patients with endocarditis. More information is needed before the widespread use of this preparation can be recommended. It is to be anticipated that its administration will be limited to patients

requiring relatively small daily amounts of penicillin.

There seems to be no place for penicillin given orally in the therapy of subacute bacterial endocarditis since it is neither an economical nor a sure method. Five to ten times the parenteral dose must be administered by mouth in order to obtain comparable serum penicillin levels. Absorption is irregular, undependable and varies greatly in its relation to meals.

Duration of Therapy. It has been difficult to establish an optimal period of treatment for subacute bacterial endocarditis. Autopsies have been done on numerous cases in which the active infectious process apparently had been arrested prior to death due to some other cause. Analysis of the findings reveals much variation in the time required for complete healing of the vegetations. Cocci have been found by microscopic examination of the vegetations as long as three months after the completion of sixty consecutive days of penicillin therapy.[20] These have been located in small areas of necrosis and leukocytic infiltration deep in scarred and nearly healed lesions. It is of interest that cultures prepared from ground portions of these vegetations were sterile.

In contrast, other investigators[3,4,21] have not been able to demonstrate the presence of bacteria in lesions examined a few weeks after the conclusion of treatment with comparable daily amounts of penicillin given for only two to four weeks.

It is difficult to know how much importance should be attached to the knowledge that bacteria may still be present in the heart valves weeks after the infection has been clinically controlled. Accumulating evidence suggests that relapse usually occurs within days or a very few weeks of the time treatment has been stopped. If this is true, persisting foci of organisms surrounded by scar tissue may not be indicative of ultimate recurrence of the infection.

Since the study of the anatomic end result does not furnish the answer, the pooling of experience with many cases must be the guide in determining the adequate period of treatment. Evidence is now at hand which suggests that the critical factor is the dose of penicillin employed. Numerous cases have been reported in which failure has followed the administration of increasing but inadequate amounts of the drug for long periods. Then, when penicillin in quantities adequate for that particular case was given, a few days of treatment were sufficient. Some striking examples have been cited in the review of the literature previously presented.[2,3,4,7,9]

The prolonged periods of treatment given to the patients discussed in this paper now seem excessive. Those that responded promptly probably would have been cured with much briefer therapy. On the other hand, those that required multiple courses of penicillin with increasing dosages were not treated soon enough with the daily amount of penicillin required to arrest the infection. It is of utmost importance that the required curative daily dosage be employed at the earliest possible time. This will minimize the dangers of the development of increased penicillin resistance of the organism and of additional deformity of the valve during prolonged subcurative therapy. Every patient with streptococcal subacute bacterial endocarditis should receive 500,000 or more units of penicillin daily as indicated by the organism's sensitivity. The period of treatment should be approximately four weeks. This regimen will be followed by arrests of the infection in nearly all cases.[2,3,22,23,24,25] Difficult problems will be recognized much more quickly, and drastic increases promptly made in the daily amount of penicillin used if the duration of the initial course has been no longer than one month.

SUPPLEMENTARY THERAPEUTIC MEASURES

Anticoagulants. The use of heparin and, to a lesser degree, dicumarol in the therapy of endocarditis was advocated first in the era of the sulfonamide treatment of this disease. Shortly after the advent of penicillin therapy evidence indicated that benefit was derived

from the combined use of penicillin and heparin.[12] Subsequent reports, however, have revealed that no advantage is gained from the use of anticoagulants.[2,11,14] A recent communication[8] added what should be the final argument against the necessity or even advisability of employing these drugs. There was no lower incidence of embolic phenomena and, of greater importance, fresh fibrin deposits on the diseased heart valves were demonstrated at autopsy in patients who received heparin. The nature of these findings, when added to the dangers of uncontrolled hemorrhage, increased technical difficulties and much greater expense, definitely argues against anticoagulant therapy in this disease. It has been suggested that small amounts of heparin, such as 50 mg., when incorporated in a day's supply of infusion fluid may be of help in preventing local clotting in the needle and adjacent vein during continuous intravenous therapy. This is a particularly useful procedure when para-aminohippuric acid or diodrast is given.[6,7]

Renal Tubular Blocking Substances. Substances that interfere with the excretion of penicillin by kidney tubules have been employed in order to obtain higher serum levels without increasing the dose of penicillin. It has been shown that the simultaneous administration of penicillin and sodium para-aminohippurate or diodrast by continuous infusion maintains serum levels several-fold greater than those obtained when penicillin is given alone.[26,27,28] Striking clinical applications of these methods have been reported.[6,7] These preparations have not been extensively used because they are expensive and require continuous infusion. In order to overcome this last objection, benzoic acid has been administered orally.[21,29] Serum levels were obtained comparable to those to be expected from doses of penicillin six to ten times as great if given alone.

The encouraging effects derived from the use of these renal tubular blocking substances has led to further research in an effort to discover others. Clinical investigations with caronamide (4′-carboxy-phenylmethanesulfonanilide), a new oral drug, are currently in progress.[30]

Streptomycin. Because of the widespread use of streptomycin in infections due to gram-negative organisms, its effectiveness against gram-positive cocci is not appreciated. Many strains of streptococci and staphylococci are relatively susceptible or very sensitive to the action of this antibiotic.

Whenever a case of subacute bacterial endocarditis caused by a resistant organism is encountered, sensitivity studies with streptomycin should be done. The combined use of the two drugs may be effective when either given alone is not. The case of enterococcal endocarditis previously mentioned is an illustrative example.[3] The ultimate eradication of the infection in Case v was accomplished by the use of penicillin but it is not unreasonable to assume that benefit was derived from the administration of streptomycin.

Prophylaxis. The administration of sulfonamides and penicillin at the time of tooth extraction, tonsillectomy and operative genitourinary procedures in all cases of known valvular or congenital heart disease is an accepted prophylactic measure against the possible development of subacute bacterial endocarditis. An adequate program has not yet been established. Hunter[23] reports the disease following tooth extraction in a patient who had received full doses of sulfadiazine and 25,000 units of penicillin every three hours for two days. He and his colleagues now give 100,000 units every three hours with full doses of sulfadiazine for two days, and then continue the sulfadiazine alone for several additional days.

CONCLUSIONS

The infectious process can be arrested in nearly every case of non-hemolytic streptococcal subacute bacterial endocarditis if enough penicillin is administered in each twenty-four-hour period. Nine cases have been presented, each of which has received

from 1 to 12 million units of the antibiotic daily. Eight patients have recovered.

Some definite recommendations for the treatment of this disease have been derived from the analysis of these cases and from those reported by others. The *in vitro* penicillin sensitivity of the causative organism should, if possible, be determined before therapy is instituted. The initial daily dosage of penicillin should be based on these studies. Cases with sensitive organisms should receive at least 500,000 units per day. When the causative organism is moderately or markedly resistant, 1, 5, 10 or even 20 million units should constitute the daily dosage.

The duration of therapy should be approximately four weeks. More prolonged therapy is usually unnecessary if adequate amounts of penicillin are used, and increased resistance of the organism to penicillin may develop under prolonged subcurative dosage.

The daily penicillin dosage should be drastically increased five- to ten-fold if the circulating blood is not promptly sterilized after treatment has been started or if relapse occurs subsequent to its completion. There will be instances of unnecessarily intensive therapy but arrest of the infection should more nearly approach 100 per cent.

The drug may be effectively administered by continuous drip or intermittent intramuscular injections. The latter method is more simple and very large individual doses of crystalline penicillin can be given with minimal local discomfort. The use of anticoagulants is not indicated. Streptomycin may advantageously be used alone or simultaneously with penicillin in some very resistant cases.

ADDENDUM

One year after submitting this article, all eight of the living patients remain free from any evidence of recurrent infection.

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Expulsion of Group A Hemolytic Streptococci in Droplets and Droplet Nuclei by Sneezing, Coughing and Talking*

MORTON HAMBURGER, JR., M.D. *and* O. H. ROBERTSON, M.D.

Cincinnati, Ohio *Chicago, Illinois*

THE number of group A beta hemolytic streptococci† which carriers expelled into sterile handkerchiefs when they sneezed, coughed or blew their noses was determined in investigations among army personnel in 1944 and 1945.[1] These studies revealed that nasal carriers frequently discharged hundreds of millions of hemolytic streptococci into handkerchiefs when blowing their noses. Sneezing expelled far fewer, the output of single sneezes of throat carriers ranging from none to 106,000 and of nasal carriers from none to 50,000,000. Most coughs were entirely free of these bacteria although rare coughs dispersed 40,000 to 50,000.

Although these experiments afforded information about the maximum number of hemolytic streptococci which might be discharged by the three respiratory activities studied, they gave no indication as to whether organisms sneezed or coughed were propelled through the air far from the carrier, whether they were largely contained in heavy droplets which fell rapidly to the floor, or whether they remained floating about in the form of "droplet nuclei."[2] Furthermore, in several instances the hemolytic streptococci recovered from handkerchiefs held over the mouth during sneezing (nasal and oral sneeze discharges were collected in separate handkerchiefs) greatly exceeded the total numbers which could be accounted for by the atomization of many cc. of the carrier's saliva, the beta streptococcal content of which had been ascertained. It seemed likely that this discrepancy could be explained by contamination of the mouth handkerchief with non-atomized secretions which issued from the nose during sneezing. Thus it appeared that the number of hemolytic streptococci propelled directly into the air in either heavy or light droplets might be much smaller than the number collected by a handkerchief held over the mouth.

Although sneezing and severe coughing are not ordinarily important symptoms of streptococcus carriers,[1,3] it nevertheless seemed desirable to amplify the earlier studies in order to ascertain how many streptococci may actually be expelled into the air during these activities as well as by talking, a more common although less violent exercise. Studies of this nature were made possible by the availability, at the University of Chicago, of rooms especially designed[4] for the investigation of air-borne infection, and by the cooperation of the members of Epidemiology Unit No. 13 at the Great Lakes Naval Training Station who provided the subjects.

These experiments seemed particularly desirable because there are no recorded data upon the expulsion of any respiratory pathogen in the form of tiny droplet nuclei which may remain suspended in the air. Because of the ease with which it can be

† The terms group A streptococci, beta hemolytic streptococci and hemolytic streptococci are used interchangeably in this paper and indicate group A hemolytic streptococci.

* From the Commission on Air-Borne Infections, Army Epidemiology Board, Office of the Surgeon General, United States Army, and the Department of Medicine, University of Chicago, Chicago, Ill.

identified in air cultures, beta hemolytic streptococcus is a particularly satisfactory micro-organism with which to initiate investigations of this important problem. Bloomfield and Felty[5] in 1923, and later Paine,[6] Hare,[3] Duguid[7] and ourselves[1] investigated the number of beta hemolytic streptococci expelled by coughing, talking or sneezing upon blood agar plates, but since a blood agar plate collects a disproportionately large sample of rapidly falling particles as opposed to "droplet nuclei,"[8] it yields little or no information about the latter. Hare[3] hoped he had overcome this objection by placing plates in front of the subject at different angles from the vertical, but even this technic does not dispose of the possibility that very tiny particles may not stick to the plate.

During the winter of 1945 to 1946 we carried out a series of experiments with two objects in view: (1) to determine the numbers of group A hemolytic streptococci expelled directly into the air by sneezing, coughing and talking, and (2) to differentiate between streptococci contained in rapidly falling droplets, and tiny droplet nuclei which remain in the air for longer periods of time. It is the purpose of this communication to describe these investigations.

MATERIAL AND METHODS

Subjects. The carriers were young men between seventeen and twenty years of age undergoing primary (boot) training at the Great Lakes Naval Training Station, Illinois. They were detected by nose and throat culture surveys made by the personnel of Epidemiology Unit No. 13. Carriers exhibiting nose and throat cultures strongly positive for hemolytic streptococci or else strongly positive throat but negative nose cultures were selected for study. A few cultures were only moderately or weakly positive. Some of the carriers had been recently hospitalized for tonsillitis or pharyngitis, others had reported to sick call but had not been hospitalized and still others denied symptoms of recent respiratory infection.

Plan of Experiments. The subject, who wore a clean surgical gown, was seated in a chair in the corner of a 640 cubic foot glass-walled room, the dimensions of which were 8 by 10 feet by 8 feet high. He faced the opposite corner. The door of the room was closed and the fan customarily employed to mix the air was not run. Six air cultures (Fig. 1) were taken, as follows: (1) Three large blood agar plates (154 sq. cm. area) containing 1:1,000,000 gentian violet were placed on the floor directly in front of the subject, one 1.5, one 5.5 and one 9.5 feet from the vertical plane of his face. Large rapidly falling droplets would be expected to fall on these "settling plates," particularly the one nearest the subject. (2) In order to capture tiny "droplet nuclei" which might remain in the air longer and not settle on the plates during the course of the experiment, three broth bubbler samplers of the type described by Lemon[9] were set up 1.5, 5.5 and 9.5 feet from the subject's face, mounted on ring stands with the air inlets 3 feet from the floor. These samplers draw air through 20 cc. of broth at the rate of 1 cubic foot a minute; at the end of the experiment 5 cc. aliquots of the broth were used for making blood agar pour plates containing 1:1,000,000 gential violet, a concentration which permits alpha and beta hemolytic streptococci to grow while suppressing most staphylococci and other gram-positive saprophytes.

Immediately before the experiment, nose and throat swab cultures were made on each subject as well as quantitative cultures of the saliva, the hands and of sterile handkerchiefs into which they blew their noses. At the beginning of the experiment the investigator opened the plates, left the room, closed the door and gave the subject a signal from outside to sneeze, cough or talk. As soon as the respiratory activity being tested began the pumps used to draw air through the bubbler samplers were turned on from outside the room. The samplers were run for five minutes. The subject then left the room and in some of the sneezing and coughing tests fresh samplers were substituted for the first six. The second set of samples was started eight to eleven minutes after the first sneeze or cough. In a few tests the air was also sampled at twenty minutes, thirty minutes or three hours after the beginning of the experiment.

Sneezing. Sneezing was induced by the powdered seedpods of the prickly nightshade (Solanum eleanifolium).[1] The powder was placed on a small piece of gauze and sniffed into the nostrils by the subject. One to twenty-four sneezes were induced in five minutes in

susceptible subjects but many failed to sneeze at all.* The carriers were instructed to try to sneeze in a horizontal direction and if possible not to lower the head. This instruction was practically always adhered to. They were also cautioned not to cover the sneeze with the hand or handkerchief although a well developed reflex required voluntary control in every instance.

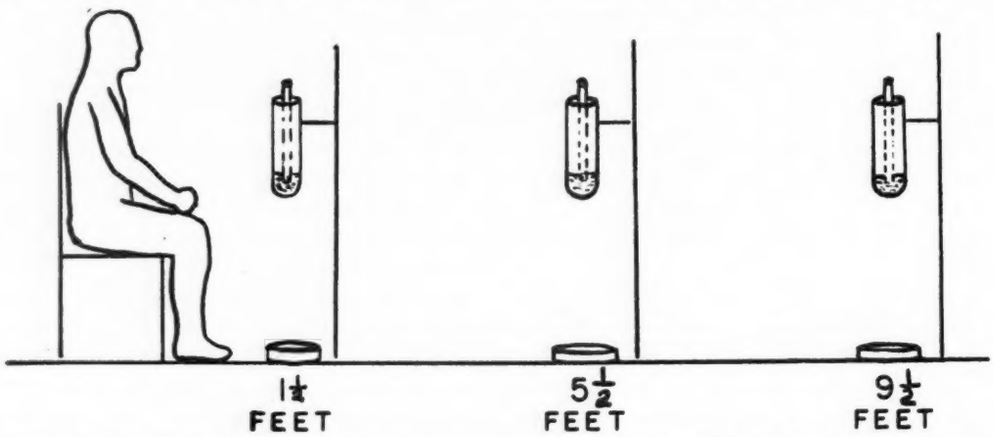

FIG. 1. Arrangement of subject and samplers during tests of sneezing, coughing and talking in experimental room. The blood agar plates on the floor captured large, rapidly falling droplets during the five-minute test. The "bubbler samplers," whose inlets were on a level with the carrier's face, captured tiny "droplet nuclei."

Coughing. Subjects were instructed to cough violently twelve times in a horizontal direction. It was observed that most of the men coughed from the back of the mouth and did not tend to approximate the teeth or lips.

Talking. Subjects counted out loud for five minutes, reaching 200 to 400 in this time. Since the numbers from one to one hundred include many beginning with F, S and T, three of the four syllables known to produce the largest number of droplets,[10] the test was weighted to some extent in favor of the greatest expulsion of bacteria.

Typing of Streptococci. The serologic type of beta hemolytic streptococci in the nose or throat of the carriers was determined by the staff of Epidemiology Unit No. 13 by the method of Swift, Wilson, and Lancefield.[11]

EXPERIMENTAL RESULTS

Cultures of the Air during Sneezing. That sneezes vary considerably in the number and size of beta streptococcus-containing droplets they produce is shown by the data of Table 1 and illustrated diagrammatically in Figure 2. Four more or less distinct bacteriologic patterns were found among the twenty subjects investigated, although the sneezes all looked very much alike to the observer stationed outside the room. In the most common pattern (65 per cent of the subjects) few or no beta streptococci were discharged as droplet nuclei, but many were expelled in large droplets captured by the settling plate on the floor 1½ feet from the subject. Fewer than 10 per cent of these large droplets travelled as far as 5½ feet. In a less common pattern, (A in Table 1), 10 per cent of the subjects, small numbers of droplet nuclei contained beta streptococci but none were collected in large droplets falling on the settling plates. In 20 per cent of the subjects, (B in Table 1), few or no beta streptococci were recovered at all.

Only one carrier, No. 20, sneezed large numbers of beta streptococci (and also alpha streptococci), both as droplet nuclei and in large droplets falling on all three settling plates. That this subject was really an unusually good atomizer was shown by a second test performed six days after the first. In these two tests he expelled an average of nine beta streptococci per cubic foot per sneeze as droplet nuclei fairly evenly

* M. J. Green had previously observed that sneezing was more easily induced in carriers whose nose cultures were positive than in those exhibiting negative nose cultures. This suggests that the irritating effect of the powder is greater on an inflamed than on an uninflamed mucous membrane.

TABLE 1

BETA HEMOLYTIC STREPTOCOCCI EXPELLED INTO AIR DURING INDUCED SNEEZING

The Most Common Pattern—Most Beta Streptococci Fell to the Floor 1½ Feet from Sneezer; Very Few Were Discharged in the Form of Droplet Nuclei

Carrier No.	TC	RN	LN	Saliva BHS per cc.	No. of Sneezes	Droplet Nuclei BHS per cu. ft. of air per sneeze.* Distance from Carrier, Feet			Large Droplets BHS per Settling Plate per sneeze. Distance from Carrier, Feet		
						1½	5½	9½	1½	5½	9½
1	++	0	++	.....	2	2.2	0	0.4	1.0	0	0
2	+++	+++	+++	470,000	6	0.3	0	0.6	1.5	0	0
3	+++	+++	+++	1,340,000	1	0.8	1.6	0	15.0	3.0	1.0
4	+++	++	+++	2,880,000	2	0.4	....	0.8	14.5	....	0.5
5	+++	+++	+	1,720,000	5	0.5	0	0	11.2	0	0
6	++	+	+++	70,000	1	0	0	0.8	11.0	1.0	0
7	+++	0	0	86,000	2	0	0	0	5.0	0	0
8	+	0	++	440,000	2	0	0	0.4	29.0	2.5	0.5
9	+++	+++	+++	31,000	3	0.5	0	0	2.7	0	0.3
10	+++	+++	+++	2,070,000	7	0.1	0.1	0	6.0	0	0
11	+	0	+++	420,000	24	0.5	0.1	0	22.0	1.4	0
12	++	++	+	80,000	3	0.3	0.3	0	6.3	0.7	0
13	+++	+++	+++	290,000	6	0.2	0.5	0.3	66.6	0.8	0
Less Common Patterns—A. More Than One Streptococcus per Cubic Foot of Air as Droplet Nuclei But None in Large Droplets											
14	++	+++	++	.....	4	1.5	0.9	0.7	0	0	0
15	+++	+	0	290,000	1	1.2	1.2	1.2	0	0	0
B. Very Few Streptococci Expelled in Any Form											
16	+	+	+++	prob. 0	3	0	0	0	0.3	0.3	0
17	++	+	+++	800,000	1	1.0	0	0	0	0	0
18	?0	++	++	?2,000,000	7	0	0	0	0.5	0	0
19	+	0	+++	500,000	1	0.8	0	0	0	0	0
Rare Pattern—Very Large Numbers of Streptococci Discharged in Both Large Droplets and Droplet Nuclei											
20†	++	0	0	7,560,000	7	10.3	7.8	3.1	86.8	65.7	23.2
20	+++	0	+	3,230,000	9	10.4	14.5	6.4	508.3	64.4	12.9
20	+++	+	++	1,200,000	4	0	0	0	32.5	1.3	0.3

TC = Throat culture
RN = Culture of right nostril
LN = Culture of left nostril
BHS = Beta hemolytic streptococcus
* Air cultured by bubbler samplers (9).
† Three separate tests were performed on Carrier No. 20 on different days

Streptococcus Types:
Type 19; cases 1, 3, 5, 8, 9, 11, 14, 15, 16, 18
Type 17; cases 6, 7, 19
Type 3; cases 10, 12, 13, 20
Not 3, 17 or 19; cases 4, 17

Nose and throat cultures were graded as follows:
+++—strongly positive
++—moderately positive
+—weakly positive
0—negative for beta hemolytic streptococci

distributed among the three bubblers. In a third experiment the following week his output diminished. He apparently combined the quality of efficient atomization with an inordinately high beta streptococcal contamination of the saliva, exhibiting the second highest contamination of any sample measured during three years' observations.

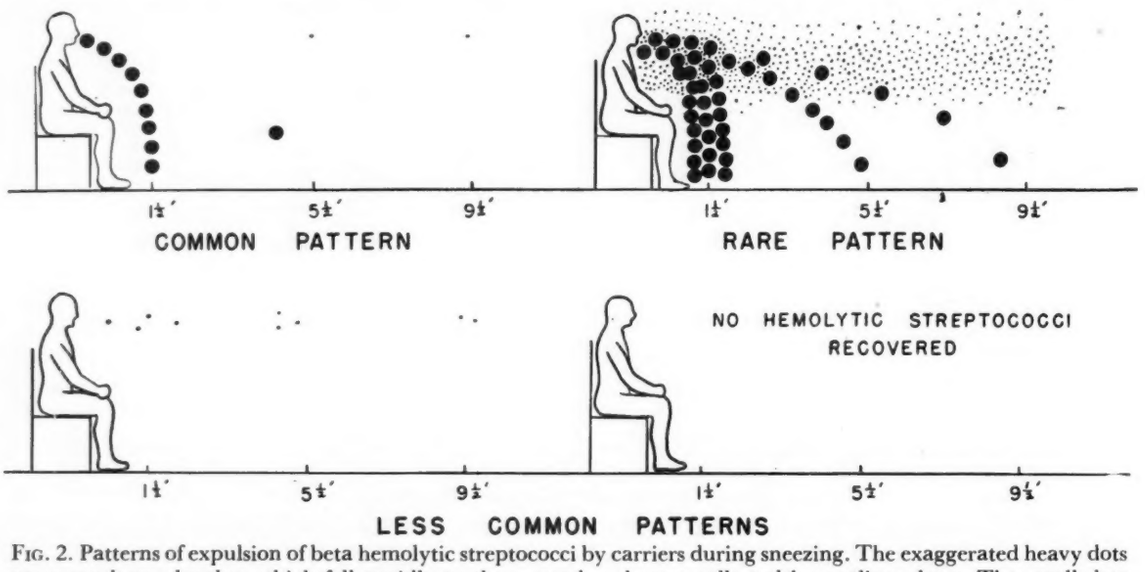

FIG. 2. Patterns of expulsion of beta hemolytic streptococci by carriers during sneezing. The exaggerated heavy dots represent large droplets which fell rapidly to the ground and were collected by settling plates. The small dots represent "droplet nuclei" which remained suspended in the air for longer periods of time. The "less common pattern" on the left is referred to in the text as "A"; that on the right as "B."

Alpha Streptococci and "Total Bacteria." In addition to the beta streptococci, green-forming colonies (salivary streptococci) were usually counted in the pour plates made from bubbler air samples as were the total number of colonies (exclusive of beta streptococci) on the gentian violet blood agar plates exposed on the floor. Although usually more than 80 per cent of the colonies on these settling plates were small green pigment producers, there were also some staphylococci and other micro-organisms which were not identified. For the purposes of this discussion it will be assumed that green-forming colonies in bubbler samples and most of the "total bacteria" on the settling plates were alpha streptococci. Only a negligible error is introduced by this assumption.

The numbers of these non-pathogens recovered from the air are presented in Table II. The most important difference between the sneeze patterns of alpha and beta streptococci was that although the discharge of great numbers of beta streptococci as droplet nuclei was rare, the expulsion of large numbers of alphas in this form was common, occurring in 35 per cent of the subjects. Most of the remaining 65 per cent expelled few or no alphas as droplet nuclei but significant numbers in large droplets. Thus the common and rare patterns but not the less common patterns of beta streptococcus expulsion were reproduced by alpha streptococci. The relations of these observations to the concentration of alpha and beta streptococci in the saliva will be discussed later in the paper.

Uniformity of Distribution of Droplet Nuclei Sneezed into the Experimental Room. Nearly as many droplet nuclei were recovered 5½ and 9½ feet from the sneezer as 1½ feet away. This distribution was in striking contrast with that of the larger droplets, 90 per cent of which travelled only 1½ feet. Figure 3 compares the number of alpha streptococci captured by bubblers and settling plates, using the counts at 1½ feet as one hundred. The figure includes all carriers who expelled as many as ten alpha strepto-

cocci per cubic foot of air per volley of sneezes.*

Persistence of Alpha and Beta Streptococci in Air after Sneezing. The persistence of alpha and beta streptococci as droplet nuclei after large droplets have left the air is illustrated by the data of Table III. This table presents cultures made during sneezing and eleven to sixteen minutes after the first sneeze, i.e., after the subject had left the room. Five experiments from two carriers are included. Two points seem worthy of comment. First, approximately 50 per cent of the number of streptococci collected during sneezing still remained suspended in the air ten to sixteen minutes. Air cultures made in one experiment thirty minutes after the first sneeze, not included in the table, revealed only 5 per cent left. The pooled data of several other experiments in which only small numbers of streptococci were expelled substantiate the findings in the two carriers discussed previously. Our findings are in general agreement with those of Bourdillon, Lidwell and Lovelock,[12] who noted that of the total number of air-borne bacteria recovered during the first minute after sneezing, 32 per cent were present fifteen minutes later.

TABLE II
ALPHA STREPTOCOCCI AND TOTAL BACTERIA EXPELLED DURING INDUCED SNEEZING

Carrier No.	No. of Sneezes	Droplet Nuclei Alpha Streptococci per cu. ft. of Air per Sneeze.* Distance from Carrier, Feet			Large Droplets Bacteria per Settling Plate per Sneeze. Distance from Carrier, Feet		
		1½	5½	9½	1½	5½	9½
19	1	189.0	224.0	197.0	438.0	91.0	98.0
7	2	53.5	41.5	158.5	2500.0	168.0	140.0
13	6	23.5	39.5	21.8	629.3	127.3	63.5
12	3	66.0	37.3	15.3	401.3	58.3	17.6
20	7	28.1	13.0	5.2	TMC	128.1	121.7
	9	10.7	21.6	4.2	TMC	77.3	32.2
	4	.....	.....	.....	163.5	16.2	8.5
5	5	10.6	9.0	6.0	248.8	36.8	8.4
16	3	28.3	5.6	2.6	18.6	12.0	1.3
8	2	7.5	3.0	7.0	76.0	5.2	3.0
9	3	4.0	2.0	.....	532.0	31.3	23.0
18	7	1.4	2.5	0.7	11.0	1.4	0.5
4	2	3.0	.....	3.5	190.0	.....	1.5
1	2	1.4	1.4	3.4	6.0	0	4.0
6	1	3.0	0	0.8	45.0	6.0	1.0
17	1	0	0	3.0	59.0	7.0	2.0
3	1	.....	.....	.....	58.0	15.0	13.0
11	24	0	0	0	1.7	0.2	0
10	7	0	0	0	42.8	0.4	0.7
2	6	0.2	0	0.6	1.5	0	0
14	4	.....	.....	.....	6.2	0	0
15	1	.....	.....	.....	9.0	4.0	5.0

TMC = Too many to count
* Air cultured by bubbler samplers[9]
The carriers in this table are the same as those in Table I

The second point of interest in Table III is the sharp change in the distribution of the streptococci on the three settling plates ten to sixteen minutes after sneezing as compared with the sneezing period. During sneezing, about ten times as many streptococci were collected in the nearest settling plate as in either of the other two whereas the three plates exposed ten to sixteen minutes after sneezing recovered approximately equal numbers. This means that the plates in the postsneezing period probably collected particles of the same order of size as did the bubblers during sneezing. Once the rapidly falling droplets had left the air, settling plates collected small droplets or droplet nuclei which had become evenly dispersed throughout the room and settled slowly to the floor.

Effect of Baffling a Sneeze with the Hand. The effect of baffling a sneeze with the hand tested by carrier No. 20, the only subject who dispersed large numbers of beta hemolytic streptococci. In a volley of nine sneezes he expelled eleven per cubic foot per sneeze (as droplet nuclei). In this volley the settling plates at 1.5, 5.5 and 9.5 feet collected 508, 64 and 13 beta streptococci, respectively, per sneeze. The alpha streptococci and total bacteria followed the same pattern although they were more numerous than the beta streptococci.

About fifteen minutes later in a different room he sneezed three times, covering his

* The same distribution maintained for beta streptococci although only one carrier expelled significant numbers of these organisms in the form of droplet nuclei.

mouth and nose with his hand. In contrast with the unbaffled sneezes two of the bubblers recovered no bacteria and the third only 0.8 beta and 1.6 alpha streptococci per cubic foot for the volley of three sneezes. Except for three colonies of beta streptococci in the nearest settling plate no bacteria of any kind were recovered by plates.

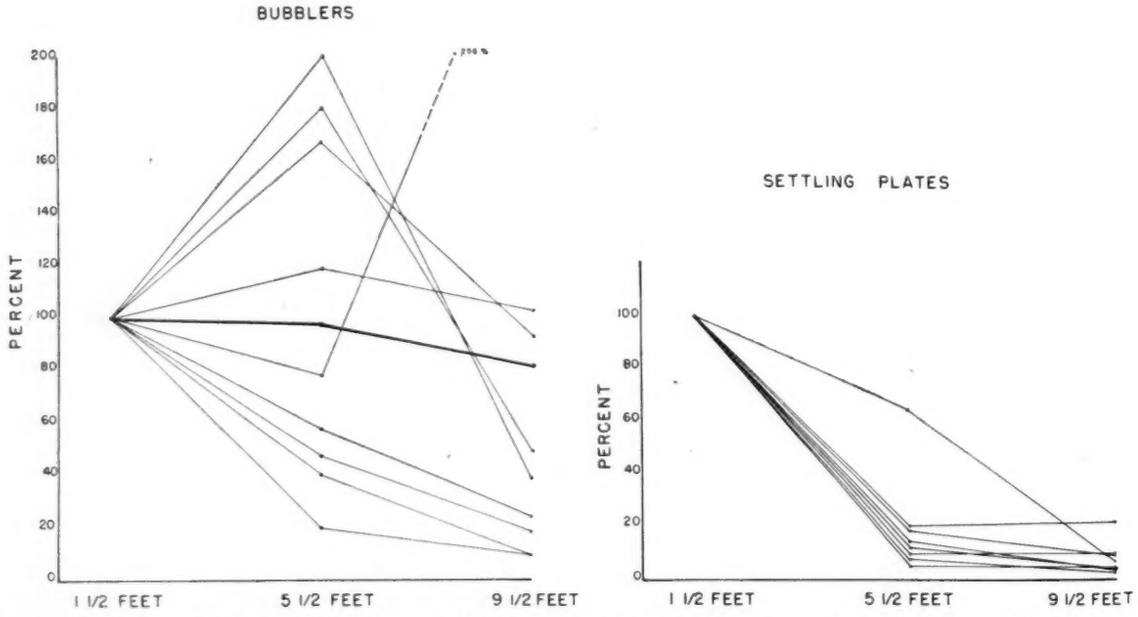

FIG. 3. Recovery of alpha streptococci expelled during sneezing at various distances from the sneezer. The number of alpha streptococci recovered 1½ feet from each subject is represented as 100 per cent. Each experiment is represented by one curve on each graph. The heavy line on the bubbler graph represents the average of the nine experiments. On the settling plate graph there are eight instead of nine individual curves because two are superimposed.

Coughing. Practically no beta streptococci were coughed out by nineteen of the twenty carriers presented in Table IV. Sixty per cent expelled none at all in either droplets or droplet nuclei in volleys of ten to seventeen vigorous unbaffled coughs. Thirty-five per cent dispersed fewer than one per cubic foot in any of the three bubbler samples, and only one or fewer in the nearest settling plate.

One carrier, No. 21, expelled very large numbers, averaging 4 per cubic foot per cough, or 45 per cubic foot during the volley of twelve coughs. Quite large numbers were recovered by both bubblers and plates 5½ and 9½ feet from the cougher. Interestingly enough the air contained no alpha streptococci, indicating that the fluid coughed was not saliva but rather material from the posterior pharynx. It is possible that this represented secretion which descended from the nose for a sterile handkerchief into which he blew his nose (not in the experimental room) shortly before the test yielded 24,000,000 beta streptococci. On the other hand, his saliva contained only 38,000 per cc. Further evidence that the saliva is not ordinarily the fluid which comprises cough droplets was the absence of alpha streptococci in the air in nearly all the other cough tests.

Talking. Almost no beta (or alpha) streptococci were expelled during talking. (Table V.) No bubbler sample collected as many as one streptococcus per cubic foot, and twenty-nine of the thirty samplers in tests of ten carriers captured none at all. The settling plates likewise were practically free of streptococci, only three of thirty plates exhibiting one colony each.

COMMENTS

Dispersion of a particular pathogen by any respiratory activity, such as sneezing, coughing or blowing the nose, will depend upon the nature of the secretion discharged

TABLE III

PERSISTENCE IN AIR OF DROPLET NUCLEI SNEEZED INTO THE EXPERIMENTAL ROOM

Carrier No.	No. of Sneezes	Kind of Streptococcus	Time of Cultures in Relation to Sneezing	Streptococci in Droplet Nuclei per cu. ft. Air per Volley of Sneezes* Distance from Carrier, Feet			Streptococci Collected on Blood Agar Plates on the Floor Distance from Carrier, Feet		
				1½	5½	9½	1½	5½	9½
7	2	Alpha	During sneezing;	107	83	317	5,000	336	280
			10–15 min. after	146	140	160	58	60	50
20	7	Beta	During sneezing;	72	55	22	608	460	163
			11–16 min. after	38	34	24	42	27	29
20	7	Alpha	During sneezing;	197	91	37	6,000	879	852
			11–16 min. after	45	35	15	196	168	132
20	9	Beta	During sneezing;	94	131	58	4,575	580	116
			11–16 min. after	18	50	22	44	41	38
20	9	Alpha	During sneezing;	97	195	38	6,000	696	290
			11–16 min. after	19	36	10	122	89	95

* Air cultured by bubbler samplers (9).

TABLE IV

BETA HEMOLYTIC STREPTOCOCCI EXPELLED BY CARRIERS DURING COUGHING

Carrier No.	TC	RN	LN	Saliva BHS/cc.	No. of Coughs	Droplet Nuclei BHS per cu. ft. of Air per Cough* Distance from Carrier, Feet			Large Droplets BHS per Settling Plate per Cough Distance from Carrier, Feet		
						1½	5½	9½	1½	5½	9½
21	+++	+	+++	38,000	12	3.3	2.9	5.5	10.9	6.5	6.0
22	++	++	++	70,000	17	0	0.1	0	1.0	0.1	0
23	++	+++	+	1,080,000	12	0.1	0	0	0.2	0	0
24	++	+++	.....	210,000	12	0	0	0.1	0	0	0
25	+++	++	+++	710,000	12	0.1	0	0	0.2	0	0
26	++	++	+++	780,000	12	0	0	0	0.2	0	0
27	+++	0	0	880,000	12	0	0	0.1	0	0	0
28	+++	0	0	780,000	12	0	0	0.1	0	0	0
29	+++	+++	0	53,000	15	0	0	0	0	0	0
30	++	++	+++	2,000	10	0	0	0	0	0	0
31	++	0	++	8,000	13	0	0	0	0	0	0
32	++	+	+	40,000	12	0	0	0	0	0	0
33	+++	+++	++	400,000	12	0	0	0	0	0	0
34	+++	0	0	160,000	15	0	0	0	0	0	0
35	+++	0	0	6,000	12	0	0	0	0	0	0
36	+++	0	0	10,000	13	0	0	0	0	0	0
37	++	0	0	360,000	12	0	0	0	0	...	0
38	+++	0	0	160,000	12	0	0	0	0	0	0
39	++	0	0	760,000	16	0	0	0	0	0	0
40	+++	+	++	200,000	14	0	0	0	0	0	0

TC = Throat culture
RN = Culture of right nostril
LN = Culture of left nostril
BHS = Beta hemolytic streptococci
* Air cultured by bubbler samplers (9)

by the activity, upon the concentration of the pathogen in the secretion and upon the mechanics and frequency of the activity. Proper understanding of the transmission of the different infections contracted via the respiratory tract must ultimately be based upon a knowledge of these factors as they bear upon each disease.

TABLE V

HEMOLYTIC STREPTOCOCCI EXPELLED BY CARRIERS WHILE COUNTING FROM 1 TO 200–400 IN FIVE MINUTES IN A LOUD VOICE

Carrier No.	TC	RN	LN	Saliva BHS/cc.	Droplet Nuclei BHS per cu. ft. of Air* Distance from Carrier, Feet			Large Droplets BHS per Settling Plate Distance from Carrier, Feet		
					1½	5½	9½	1½	5½	9½
26	++	++	+++	780,000	0	0	0	0	0	0
39	++	0	0	60,000	0	0	0	0	1	0
41	+++	+++	+++	31,000	0	0	0.8	0	0	1
42	+++	0	+	780,000	0	0	0	1	0	0
43	+++	+	+++	80,000	0	0	0	0	0	0
44	+++	+	++	.....	0	0	0	0	0	0
45	++	0	++	230,000	0	0	0	0	0	0
46	+++	++	+++	2,800,000	0	0	0	0	0	0
47	++	+	0	54,000	0	0	0	0	0	0
48	+++	0	++	14,000	0	0	0	0	0	0

TC = Throat culture
RN = Culture of right nostril
LN = Culture of left nostril
BHS = Beta hemolytic streptococci
* Air cultured by bubbler samplers (9)

Let us consider sneezing and hemolytic streptococcal infection. Two separate secretions are associated with a sneeze: the fluid nasal secretion which is not propelled violently into the air and the oral secretion which is expelled at high velocity. Although most of the nasal component is discharged either in heavy masses or as fluid which must be removed with a handkerchief, a little may occasionally be atomized as droplets.[13] The oral secretion, however, is saliva as attested by three kinds of evidence: (1) large numbers of salivary streptococci can be recovered from the air into which people have sneezed,[14] (2) stroboscopic photographs indicate that the oral sneeze discharge originates in the front of the mouth[10] and (3) sneeze discharges collected in empty dishes have the physical appearance of saliva.* The number of group A streptococci in the saliva of carriers varies from fewer than 100 per cc. to, in exceptional instances, more than 1,000,000.[15]

Contrary to popular belief, sneezing usually produces very little direct pollution of the air by beta hemolytic streptococci. In the present study of twenty carriers, only one discharged large numbers of these bacteria as tiny droplet nuclei during violent unbaffled sneezing although of course a carrier such as this one represents a real hazard. He possessed the two important requisites for the expulsion of large numbers of hemolytic streptococcus-containing droplet nuclei during sneezing: an unusually high contamination of the saliva (7,000,000 per cc.) and a mechanically efficient atomizing capacity.

In the case of most carriers the greatest proportion of the streptococci expelled in saliva during sneezing fall rapidly to the ground and hence do not contaminate the air until they are resuspended as dust. Sneezing, moreover, contributes relatively little to the bacterial reservoirs in dust, bedclothing and elsewhere in the environment because it is not a common symptom in carriers.†

Variability in the mechanical efficiency of sneezing among different subjects, brought out clearly by stroboscopic photographs,[10] is confirmed by the patterns of expulsion of alpha (salivary) streptococci. Since the concentration of these saprophytes in the saliva is remarkably constant from person to person,‡ the number recovered from the air into which someone has sneezed is a good index of the quality of his sneezes.

Of even greater importance is the relative number of bacteria expelled in tiny droplet

* Several carriers sneezed into empty petri dishes following which the amount of saliva discharged was measured. The expulsion during one sneeze ranged from less than 0.01 to as much as 0.6 cc.

† The major contribution to these environmental reservoirs comes from the gross contamination of the hands which occurs when a nasal carrier blows his nose.[1]

‡ The number of alpha streptococci per cc. of saliva varies between 7,000,000 and 40,000,000 with an average of perhaps 20,000,000. This is many times greater than the concentration of beta streptococci in saliva.

nuclei as compared with rapidly falling droplets. The fact that 35 per cent of the carriers in this series sneezed large numbers of alpha (salivary) streptococci as droplet nuclei indicates that expulsion of these tiny nuclei by sneezing is a frequent occurrence. However, it seems probable that commensal bacteria are present in only a small proportion of droplet nuclei expelled by any respiratory activity[16,17] and that group A hemolytic streptococci are contained in a still smaller proportion. This situation may prove to be different with virus particles which because of their small size may occupy a larger proportion of droplet nuclei than do bacteria. The recent experiments of Duguid[17] are interesting in this connection. He painted the inside of the mouth and fauces with congo red, then collected droplet nuclei on an oiled slide, placed in a slit sampler,[18] as the nuclei were expelled during various expiratory activities. This technic enabled him to estimate the total number of nuclei expelled regardless of whether or not they contained bacteria. In a series of tests (apparently conducted with one subject) he counted from a few hundred thousand to a few million droplet nuclei after a single natural sneeze. Such studies emphasize the need for data upon the concentration of viruses in the saliva, and upon the frequency of sneezing among carriers of the virus under consideration.

Coughing does not ordinarily discharge saliva. A cough, because it originates in the back of the throat, disperses the secretions of the pharynx, the secretions of the nose if they have dripped back into the throat or material from below the larynx. This is confirmed bacteriologically by the absence of salivary streptococci from the air into which carriers coughed. The explanation of the failure of 95 per cent of carriers to expel beta streptococci by coughing, even though they were present in large numbers in the throat, is probably that the act of coughing, even volleys of twelve violent coughs, does not ordinarily shear off enough fluid from the mucous membranes of the posterior pharynx to carry significant numbers of these organisms. This explanation is in keeping with an observation reported by Bloomfield and Felty[5] in 1923, that although they could collect few or no beta streptococci on blood agar plates held close to carriers' faces during coughing, they could obtain fairly large numbers from "hawking," an activity which presumably exerts a more efficient shearing action.

Previous studies have shown that carriers exhibiting positive nose cultures for hemolytic streptococci were more likely to transmit infection than those with positive throat but negative nose cultures.[19] Further investigation indicated that such carriers disseminate the streptococci in highly contaminated nasal secretion which reaches the environment chiefly via the hands when the carrier blows his nose.[1] Streptococci discharged in this manner contaminate handkerchiefs, clothing, bedclothing and dust and are thrown into the air when these reservoirs are agitated. Streptococci may also be transferred by direct contact with contaminated objects in the environment or, occasionally, discharged directly into the air in droplet nuclei from the respiratory tract.

Throat carriers whose nose cultures were negative were also occasionally found to be responsible for secondary cases of streptococcal infection.[19] Carrier No. 20 of this present series, who sneezed very large numbers of hemolytic streptococci, exhibited negative nose cultures at the time of the test although the nose cultures had been positive a few days before. As mentioned in the text his saliva contained an unusually high concentration of hemolytic streptococci. Such individuals, as well as some of those described in the earlier investigation of coughing and sneezing,[1] represent throat carriers who are not innoccuous.

SUMMARY

1. The numbers of beta and alpha streptococci discharged into the air of an experimental room during sneezing, coughing and talking were determined in a series of forty-eight carriers of group A strepto-

cocci. By simultaneous employment of exposed blood agar plates placed upon the floor, and "broth bubbler" samplers whose intake was 3 feet from the floor, streptococci expelled in large, rapidly falling droplets could be differentiated from those discharged as droplet nuclei which remained in the air for at least several minutes.

2. The material dispersed into the air during a sneeze is chiefly saliva.

3. Four dispersion patterns of beta hemolytic streptococci by sneezing were evident. In the most common, moderate numbers were expelled in large droplets which fell rapidly to the floor 1.5 feet from the sneezer, but very few or none in droplet nuclei. In one of two less common patterns, small numbers of beta streptococci were sneezed as droplet nuclei but none in large droplets; in the other, no beta streptococci were recovered from the air. In the rarest, of which only one example was found, large numbers of beta (and alpha) streptococci were expelled both as droplet nuclei and in large droplets; many were collected as far as 9.5 feet from the sneezer. The saliva of this carrier contained huge numbers of beta streptococci.

4. Thirty-five per cent of twenty carriers sneezed out large numbers of alpha (salivary) streptococci as droplet nuclei. Eighty per cent discharged moderate or large numbers in heavy droplets which fell rapidly to the floor.

5. About one-half the streptococci expelled into the air as droplet nuclei by sneezing were still present as long as twenty minutes after the first sneeze.

6. The material expelled during coughing apparently originates in the back of the throat or below the epiglottis and contains little if any saliva.

7. Only one of twenty carriers coughed large numbers of beta streptococci into the air as droplet nuclei or in large droplets; he expelled no alpha streptococci. Ninety-five per cent of the carriers coughed few or no streptococci collected by either type of air culture.

8. Practically no streptococci were recovered from the air of rooms while carriers counted out loud for five minutes.

CONCLUSIONS

1. Although sneezing probably accounts for a certain number of sporadic cases of hemolytic streptococcal infection, it is not, in our opinion, important in epidemics because (1) it is not a common symptom and (2) very few sneezes discharge significant numbers of beta hemolytic streptococci into the air as droplet nuclei. The rare carriers whose sneezes heavily contaminate the air may be very dangerous if they do not baffle the sneezes efficiently. Since the material atomized in a sneeze is saliva, these individuals represent a type of dangerous carrier whose nose culture may be negative.

2. Coughing, likewise, is important only in sporadic infections for similar reasons. This symptom is more common than sneezing.

3. Talking expels negligible numbers of hemolytic streptococci.

4. Since the concentration of alpha (salivary) streptococci per cc. of saliva is remarkably constant from one individual to another, the number of these microorganisms recovered from the air in large droplets or droplet nuclei during sneezing provides a good index of the quality of sneezes.

5. A more precise understanding of the rôle of sneezing in the transmission of different respiratory diseases may result from a study of the concentration of the infective agent in the saliva and of the frequency of sneezing among carriers of the agent.

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Changes in the Bacterial Flora of the Throat and Intestinal Tract during Prolonged Oral Administration of Penicillin*

MIRIAM OLMSTEAD LIPMAN, M.D., JAMES A. COSS, JR., M.D. *and* RALPH H. BOOTS, M.D.
New York, New York

IT is a well established fact that gram-positive micro-organisms, in general, are susceptible to the action of penicillin whereas most of the gram-negative organisms are relatively insensitive. The effect of penicillin administration on infectious agents within the body has been discussed in detail by a number of investigators. Little attention has been directed, however, toward its effect on the normal flora of the body. Likewise, the effect of prolonged administration has been studied to a limited extent only and predominantly in relation to Streptococcus viridans and those other organisms observed in patients with subacute bacterial endocarditis.

A clinical trial of penicillin in the treatment of arthritis[1] offered the opportunity of observing the effect of orally administered penicillin on the throat and intestinal flora of a small group of individuals over a prolonged period of time.

MATERIALS AND METHODS

Ten patients† with active manifestations of arthritis were selected for study. Nine of these were entirely free from respiratory tract infection at the time that the experiment was instituted. One patient (F. B.) had a nasal discharge possibly due to a chronic sinus infection. Three of the seven tested within one month prior to the beginning of the experiment had shown anti-streptolysin-O titers of 250 to 333 units per ml.

Amorphous penicillin (sodium salt) was used throughout the experiment. The penicillin was administered orally without buffer. Each adult received 1,000,000 units daily, in divided dosage; each child received 500,000 units daily.‡ Duration of treatment varied from four weeks to six and one-half months. Determinations of penicillin concentration in the blood were made at frequent intervals by a serial dilution method, using Streptococcus hemolyticus (strain C203MV) as the test organism.

Throat and stool examinations were made, with few exceptions, prior to, at frequent intervals during and subsequent to treatment. In culturing the throats two swabs were used, both of which were first streaked on fresh, rabbit-blood agar plates; smears were prepared with one swab; the other swab was twirled in a tube of plain broth, a dilution of which was used for seeding a blood agar pour plate. A few nose and tooth cultures were made on one patient.

Each stool specimen was examined microscopically for predominant forms and was cultured on "SS" agar for enteric organisms and on blood agar, after approximately one hour's incubation in 1 per cent Na_2CO_3, for

† These patients are described in detail elsewhere.[1] Six had typical adult rheumatoid arthritis, two had rheumatoid arthritis of the spine (Marie-Strümpell spondylitis) and two had juvenile rheumatoid arthritis.

‡ The therapeutic regimen used is discussed in detail elsewhere.[1]

* From the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y. A preliminary report of this work was presented before the Society of American Bacteriologists, Detroit. Michigan, May, 1946.[2]

streptococci. In many instances, specimens were cultured anaerobically as well as aerobically.

Organisms isolated were identified roughly according to general groups. Special emphasis, however, was placed on the growth in 6.5 per cent NaCl broth. For convenience all strains viable in blood broth after being heated at 60 to 62°c. for thirty minutes were classified as enterococci.

Most of the streptococcus and pneumococcus strains isolated, as well as many

TABLE I

PREDOMINANT THROAT FLORA PRIOR TO, DURING AND SUBSEQUENT TO PENICILLIN THERAPY

Patient	Prior to Therapy		During Therapy		Subsequent to Therapy	
	Smear (Gram Stain)	Culture	Smear (Gram Stain)	Culture	Smear (Gram Stain)	Culture
J. P.	+	Str. viridans H. hemolyticus	−	Neisseria	+	Non-hemolytic streptococci
A. G.	+	Str. viridans D. pneumoniae	−	Coliforms* M. tetragenus Str. viridans	+	Str. viridans D. pneumoniae
F. A.	+	D. pneumoniae Str. viridans	−	Coliforms Hemophilus Neisseria	+	Str. viridans D. pneumoniae
K. P.	..	Str. viridans	−	Neisseria Hemophilus	− +	Neisseria Str. viridans
G. B.	+	Str. viridans D. pneumoniae	−	Coliforms	+	Str. viridans
M. W.	+	Staph. aureus Non-hemolytic streptococcus	−	Coliforms Neisseria	+	Streptococci
G. M.	+	Str. viridans	−	Coliforms† Enterococcus	+	Str. viridans
F. B.	−	D. pneumonia Str. viridans K. pneumoniae	−	Coliforms K. pneumoniae Neisseria	+	Micrococcus Staph. aureus
W. O.	..	Str. viridans	−	Neisseria Coliforms	− +	Str. viridans
H. G.	+	Str. viridans D. pneumoniae	−	Str. viridans‡		

* Coliforms were present in all cultures, predominant on three of five occasions. M. tetragenus was predominant once, Str. viridans once.

† Coliforms were present in all cultures, predominant on five of six occasions. An enterococcus (hemolytic) predominated once.

‡ Only one examination was made after two weeks' treatment.

gram-positive cocci. All staphylococci were tested for mannitol fermentation and for coagulase production, all pneumococci for bile solubility and some for type. Cultures from all sources were examined with special reference to Str. hemolyticus. Most of the hemolytic streptococci isolated were tested for serologic grouping.[3] Group A strains were tested for type. Streptococci from stool cultures and any other strains morphologically resembling enterococci were tested for heat tolerance, mannitol fermentation and other strains, were tested by a serial dilution method[4] for penicillin sensitivity. The sensitivity was expressed in terms of minimal concentration of penicillin required to inhibit growth of a culture diluted so as to be approximately comparable in density with C203MV, the group A hemolytic streptococcus used as standard.

RESULTS

Throat Flora. Prior to administration of penicillin, the predominance of gram-

positive cocci in all throats except one was indicated by smear or culture (Table I); in most instances results of the two examinations were consistent. Str. viridans predominated in the majority of cultures but each individual presented a characteristic throat picture, differing in the morphology of the predominant form or in the mixture of organisms present. Hemolytic streptococci were recovered from seven patients, group A strains from only two. (Table II). Diplococcus pneumoniae was recovered from five patients, type III from two, non-type-specific strains from these two and three others.

TABLE II
INCIDENCE OF THROAT CULTURES POSITIVE FOR HEMOLYTIC STREPTOCOCCI

Patient	Prior to Therapy	During Therapy	Subsequent to Therapy
J. P.	1/2 (2 strains, 1 group D and 1 unclassified*)	0/4	1/2 (untested)
A. G.	1/3 (unclassified*)	0/5	1/1 (unclassified*)
F. A.	0/3	0/5	1/2 (unclassified*)
K. P.	1/3 (group A, type 2)	1/10 (unclassified*)	0/3
G. B.	0/2	0/3	0/1
M. W.	1/3 (group A, type 38)	0/4	2/3 (group A, non-type-specific, from 1 culture, unclassified* strains from 2 cultures)
G. M.	3/3 (group F from 1, group G from 2)	1/6 (group D)	1/2 (group D)
F. B.	0/2	0/8	0/2
W. O.	1/1 (unclassified*)	0/10	1/5 (unclassified*)
H. G.	1/3 (group D)	0/1	

Numerator = number of throat cultures positive for hemolytic stretopcocci.
Denominator = number of throat cultures examined.
*"Unclassified" signifies negative grouping with antisera A-L inclusive.

During penicillin therapy a striking change in the throat flora occurred. (Tables I and III.) Smears from all ten patients and the majority of cultures from nine indicated the predominance of gram-negative forms: saprophytic Neisseria (usually chromogenic), hemophilic bacteria and coliform bacteria. A culture of H. G.'s throat two weeks after the beginning of treatment (the only examination made during her four weeks' course) presented an exception in the series, the predominance of gram-positive cocci (Str. viridans) and the absence of coliform bacteria.

The organisms classified as coliforms were lactose-fermenting, gram-negative rods forming grey, non-mucoid colonies unlike the watery growth of Klebsiella pneumoniae. In no instance were coliform colonies observed prior to the administration of penicillin. They appeared soon after the beginning of treatment, sometimes apparently in pure culture, and were observed in the majority of cultures throughout the course of therapy. (Table IV.) The pneumococci, hemolytic streptococci and hemolytic micrococci observed before treatment were absent during treatment. (Tables II, III and VI.) Strains of hemolytic streptococci different from those in the prepenicillin cultures appeared on two occasions: an enterococcus, group D, in one patient and a microaerophilic strain, which failed to group, in a second patient.

Subsequent to treatment the flora showed an increase in the variety of organisms present and became predominantly gram-positive again within a period of days or weeks. (Table I.) The change was demonstrated by smears and cultures from five patients in one week or less. Three patients were not examined until three weeks, five weeks and three months, respectively, at which times gram-positive organisms predominated in smears and cultures. The first postpenicillin throat culture on patient K. P., made three weeks after her course, showed mostly gram-negative forms; at the next examination, in six weeks, gram-positive organisms predominated in the smear and colonies of Str. viridans were definitely predominant in cultures. Patient H. G. had no throat examination after penicillin was discontinued.

Colonies of coliform bacteria at times appeared in postpenicillin throat cultures from seven of ten patients but were less numerous than during treatment. The time

of their disappearance varied from seven days to more than three months. (Table IV.) In the short period of observation after treatment was discontinued the incidence of pneumococci and group A hemolytic streptococci was slightly lower than before treatment. (Tables II and III.)

ment showed colonies of hemolytic Staphylococcus aureus only (coagulase and mannitol positive); similar staphylococci were recovered six and seven weeks after treatment.

Intestinal Flora. No definite change in the intestinal flora during the administration of penicillin was demonstrated by smears.

TABLE III

EFFECT OF PENICILLIN THERAPY ON THE PRESENCE OF VARIOUS ORGANISMS IN THE THROAT CULTURES OF TEN PATIENTS

Gram-positive Organisms	No. of Patients Positive			Gram-negative Organisms	No. of Patients Positive		
	Prior to Therapy	During Therapy	Subsequent to Therapy*		Prior to Therapy	During Therapy	Subsequent to Therapy*
D. pneumoniae	5	0	4	Neisseria	9	10	6
Type 3	2	0	0				
Non-type-specific	5†	0	4†	Hemophilus	4	8	5
				Hemolytic	2	5	5
Str. hemolyticus	7	2	6	Non-hemolytic	2	8	1
Group A	2	0	1				
Group F	1	0	0	K. pneumoniae	2	2	1
Group G	1	0	0				
Group D	2	1	1	Coliform bacteria	0	9	7
Group not A-L	3	1	4				
Group untested	..	..	1				
Non-hemolytic streptococci	10	9	9				
Viridans	10	6	9				
Indifferent	7	3	3				
Staphylococcus	4‡	2	3				
Micrococcus							
Colonies small, hemolytic	2	0	1				
Colonies large, grey	6	3	8				
Diphtheroid-like organisms	5	4	3				

* Only nine patients were examined subsequent to treatment.

† Four prepenicillin and three postpenicillin strains included were not completely bile soluble.

‡ Staph. aureus was recovered from a nose culture on a fifth patient.

In one patient (K. P.) Str. viridans was recovered in pure culture from a tooth extracted prior to penicillin therapy. From a culture of a tooth extracted three weeks subsequent to treatment a small hemolytic micrococcus was isolated. This organism was similar morphologically, culturally and in penicillin sensitivity to strains isolated from this patient's throat cultures before and after treatment. A nose culture before treat-

Cultures of stools, however, indicated that streptococci present before treatment were somewhat inhibited during penicillin therapy. (Table V.) In eight of nine patients examined prior to and during treatment the incidence of positive cultures was lower during the latter period. Streptococci were recovered from 75 per cent of the prepenicillin cultures, from 23.2 per cent of those examined during therapy. Few speci-

mens were cultured subsequent to treatment (eight from seven patients); all, however, were positive for streptococci. Of the fifty streptococcus strains isolated from stool cultures, forty-six (92 per cent) were heat resistant. The remaining four were negative to all of the enterococcus tests employed, that is, they were not viable after being heated at 60 to 62°C., they did not ferment mannitol nor grow in 6.5 per cent NaCl broth. One of these four strains grouped serologically as an H.

TABLE IV
INCIDENCE OF NON-MUCOID COLIFORM BACTERIA IN THROAT CULTURES

Patient	Positive Cultures			First Positive Culture during Therapy (Days)	First Negative Culture Subsequent to Therapy (Weeks)
	Prior to Therapy	During Therapy	Subsequent to Therapy		
J. P.	0/2	4/4	0/2	20	3
A. G.	0/3	5/5	1/1	9	*
F. A.	0/3	4/5	0/2	23	1
K. P.	0/3	4/10	2/3	21	3
G. B.	0/2	3/3	1/1	5	*
M. W.	0/3	4/4	2/3	18	5
G. M.	0/3	6/6	1/2	5	1
F. B.	0/2	8/8	1/2	10	3
W. O.	0/1	8/10	4/5	42	11
H. G.	0/3	0/1			

Numerator = number of throat cultures positive for coliforms.
Denominator = number of throat cultures examined.
* Cultures were still positive for coliform bacteria at the time the experiment was discontinued, five weeks (A. G.) and three months (G. B.) after penicillin therapy.

Penicillin therapy had no noticeable effect on the enteric bacilli or on the anaerobes of the intestinal tract.

Penicillin Sensitivity of Organisms Isolated. Most of the gram-positive cocci isolated throughout the study were tested for sensitivity to penicillin. Strains recovered from throat cultures prior to treatment ranged in sensitivity from 0.025 unit to 10 units. Approximately the same range, 0.05 unit to 10 units, was covered by stool strains. During treatment the organisms sensitive to less than 1 unit were recovered from only five throat cultures and from no stool cultures. Subsequent to treatment the range of sensitivity of gram-positive cocci from throat cultures was the same as before treatment. Stool strains isolated required from 1 to more than 10 units. (Tables VI and VII.)

TABLE V
INCIDENCE OF STOOL CULTURES POSITIVE FOR STREPTOCOCCI

Patient	Prior to Therapy	During Therapy	Subsequent to Therapy
J. P.	1/1	0/2	
A. G.	..	0/4	1/1
F. A.	2/3	2/5	1/1
K. P.	2/2	2/7	1/1
G. B.	1/2	1/3	
M. W.	0/2	1/4	1/1
G. M.	2/2	3/4	1/1
F. B.	1/1	2/7	1/1
W. O.	1/1	2/6	2/2
H. G.	2/2	0/1	
Total No. Patients	9	10	7
Total No. Cultures	16	43	8
Total No. Cultures Positive for Streptococcus	12	10	8
Per cent Positive for Streptococcus	75	23.2	

Numerator = number of stool cultures positive for streptococci.
Denominator = number of stool cultures examined.

Few of the gram-negative organisms isolated from either throat or stool cultures were tested for sensitivity. Of those tested, Hemophilus hemolyticus appeared to be

TABLE VI

PENICILLIN SENSITIVITY OF GRAM-POSITIVE COCCI FROM THROAT CULTURES

Patient	Isolation in Relation to Therapy	Organisms Tested										
		D. Pneumoniae		Str. Hemolyticus		Non-hem. Strep.		Staphylococcus			Micrococcus	
		Type	Sens. u./ml.	Group	Sens. u./ml.		Sens. u./ml.	Co-agu-lase	Man-nitol	Sens. u./ml.		Sens. u./ml.
J. P.	Before	....	....	Not A-L	0.05	Viridans	0.05					
				D	1.0							
	After	....	....	Untested	0.05							
A. G.	Before	N.T.	0.025	Not A-L	1.0	Viridans	0.05	−	+	0.05		
		N.T.	0.05				0.1					
	During	....	....	.....	.....	Viridans	1.0					
	After	N.T.	0.05	Not A-L	0.05	Viridans	0.05					
						Indiff.	0.1					
F. A.	Before	N.T.	0.05	.....	.....	Viridans	0.05	−	+	1.0		
		N.T.	1.0	.....	.....	Viridans	0.1					
	During	....	....	.....	.....	Viridans (Ent.)	1.0					
	After	N.T.	0.05	Not A-L	1.0							
K. P.	Before	....	....	A, type 2	0.05	Viridans	0.05	..	..	*	Hem.	0.05
						Indiff.	1.0					
						Indiff.	10.0					
	During	....	....	Not A-L	0.025	Viridans	1.0	+	+	10.0		
						Indiff.	1.0					
	After	....	....	.....	.....	Viridans	0.025	+	+	10.0	Hem.	0.1
						Viridans	1.0					
G. B.	Before	3	0.1	.....	.....	Viridans	1.0					
M. W.	Before	....	....	A, type 38	0.025	Viridans	0.05	+	−	0.1	Hem.	0.025
						Indiff.	0.05	+	−	1.0		
	After	....	....	A (N.T.)	0.025	.....	.....	+	+	0.1		
				Not A-L	0.05							
G. M.	Before	....	....	F	0.05	Viridans	0.05					
				G	0.05	Viridans	0.1					
						Viridans	1.0					
	During	....	....	D	10.0	.....	.....	−	+	0.1		
	After	....	....	D	10.0	Viridans	0.025					
						Viridans	0.05					
						Viridans	0.1					
						Viridans	10.0					
F. B.	Before	N.T.	0.05	.....	.....	.....	.....	+	+	1.0		
	During	....	....	.....	.....	Viridans	0.05					
	After	....	....	.....	.....	Viridans	1.0	+	+	0.1	..	0.025
W. O.	Before	....	....	Not A-L	0.05	Indiff.	0.05					
						Viridans	0.1					
	During	....	....	.....	.....	Indiff.	1.0					
	After	....	....	Not A-L	0.025	Viridans	0.025					
						Viridans	0.05					
H. G.	Before	3	0.1	D	0.1	Viridans	0.05					
		N.T.	0.05			Viridans	0.1					
						Indiff.	1.0					
	During	....	....	.....	.....	Viridans	0.1					
						Viridans	1.0					

N.T. = non-type-specific.

* = Staph. aureus, C+, M+, sensitive to 0.1 U penicillin, was recovered from a nose culture prior to therapy.

the least resistant, requiring from 1 to 10 units.

Concentration of penicillin obtained in the blood of these patients is discussed in detail elsewhere.[1] Peak levels varied from 0.1 unit (in J. P.) to 1.6 unit (in G. M.).

In the series of individuals described in the present report the bacterial flora of the throat prior to treatment was normal. Gram-positive organisms were predominant throughout (except in some cultures from a patient with chronic sinusitis), and those

TABLE VII

PENICILLIN SENSITIVITY OF STREPTOCOCCI FROM STOOL CULTURES

Patient	Prior to Therapy						During Therapy						Subsequent to Therapy					
	Resistance to 60–62°C.	Hemolysis	Mannitol	Growth in 6.5% NaCl	Serologic Group	Penicillin Sensitivity u./ml.	Resistance to 60–62°C.	Hemolysis	Mannitol	Growth in 6.5% NaCl	Serologic Group	Penicillin Sensitivity u./ml.	Resistance to 60–62°C.	Hemolysis	Mannitol	Growth in 6.5% NaCl	Serologic Group	Penicillin Sensitivity u./ml.
J. P.	−	−	−	−	H	0.1												
	+	−	+	+	D	1.0												
A. G.	..	..	..	..	..	.....	..	..	..	..	..	....	+	+	+	−	D	>10.0
	..	..	..	..	..	.....	..	..	..	..	..	....	+	−	+	+	D	10.0
F. A.	+	−	−	..	..	0.05	+	−	+	+	..	10.0	+	−	+	+	D	10.0
	+	−	−	..	..	1.0	..	..	..	..	..	....	+	+	+	+	D	10.0
	+	−	−	..	D	10.0												
K. P.	+	−	−	+	O	10.0	+	−	+	+	..	10.0	+	−	−	−	..	10.0
	+	−	+	..	D	10.0												
G. B.	+	−	−	−	..	0.1												
M. W.	..	..	..	..	..	.....	..	..	..	..	..	....	−	−	−	−	O	1.0
	..	..	..	..	..	.....	..	..	..	..	..	....	+	−	+	−	D	10.0
G. M.	−	+	−	..	O	0.05	+	+	+	−	D	10.0	+	+	+	−	D	10.0
	+	−	−	−	..	0.05	+	+	+	+	D	10.0						
	+	−	−	−	..	0.1	+	−	+	+	..	10.0						
	+	−	+	−	..	0.05												
	+	−	+	−	..	0.1												
F. B.	+	−	+	+	O	10.0	+	−	+	+	..	10.0	+	−	+	+	D	10.0
W. O.	+	−	−	+	D	10.0	+	−	+	+	D	10.0	+	−	+	+	D	>10.0
H. G.	+	−	+	..	..	10.0												

0 = No reaction with antisera of groups A to L, inclusive.

COMMENTS

Elimination of gram-positive pathogens from the throat during oral administration of penicillin has been reported by Keith et al.,[5] by Levitt and Leathen[6] and by others. No reports on the effect of penicillin administered orally over prolonged periods of time have come to our attention.

tested were, with one exception, sensitive to 1 unit or less of penicillin per ml. The shift from a predominantly gram-positive to gram-negative flora during penicillin therapy was striking. The significance of such a change and its possible effect upon the susceptibility of the individual to various infections remains to be determined.

Difference in the incidence of streptococcus-positive cultures prior to and during treatment seems significant although the inaccuracy of a comparative study of such material is recognized. Whereas 75 per cent of stool cultures prior to penicillin therapy were positive for streptococci, only 23 per cent were positive during therapy. The streptococcus strains isolated during treatment showed a relatively low sensitivity to penicillin.

The possible development of bacterial resistance to penicillin on low dosage or on prolonged administration of penicillin has been discussed at length by many investigators. The present study has offered opportunity to observe the effect of prolonged administration of penicillin in this connection. Comparison of similar strains recovered from throat or stool cultures before and after penicillin therapy revealed no definite evidence of an increase in resistance to the drug. All strains of pneumococci, hemolytic micrococci and hemolytic streptococci isolated from throat cultures subsequent to penicillin therapy were as sensitive as strains with similar characteristics isolated prior to treatment. Two patients showed slightly more resistant strains of Str. viridans and one patient a slightly more resistant strain of Staph. aureus after completion of the course of therapy than before treatment. However, no proof of the identity of these strains exists.

Continuous absence of gram-positive organisms, particularly streptococci, from the throat flora during prolonged penicillin administration and the apparent failure of the streptococci to acquire penicillin resistance, is of interest in connection with the problem of the prophylaxis of rheumatic fever by means of anti-streptococcal agents.

SUMMARY

A bacteriologic study of the throat and intestinal flora of ten patients with arthritis, treated orally with 500,000 to 1,000,000 units of penicillin daily over a prolonged period of time, has been carried out.

Upon administration of penicillin there was a sudden change in the bacterial flora of the throat from gram-positive to gram-negative. Coliform bacteria appeared in the throat early in the course of treatment and were present, and often predominant, throughout the course. Subsequent to treatment there was a rapid reappearance of gram-positive cocci in the throat. The coliform organisms disappeared gradually.

There was a lower incidence of streptococcus-positive stool cultures during, than prior to or subsequent to penicillin therapy.

No difference in the range of penicillin sensitivity of the gram-positive cocci isolated from throat cultures prior to and subsequent to treatment was demonstrated. Penicillin-sensitive organisms were infrequent in the throat and stool cultures during treatment.

There was no evidence that bacterial resistance to penicillin developed during the course of therapy.

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Prolonged Administration of Penicillin in Arthritis*

JAMES A. COSS, JR., M.D., ELI BAUMAN, M.D., RALPH H. BOOTS, M.D.
and MIRIAM OLMSTEAD LIPMAN
New York, New York

PREVIOUS studies of the effect of penicillin† in the rheumatic group of diseases have not been encouraging.[1–3] However, it has been reported that in other conditions due to known bacterial agents failures in treatment have often been linked with failure to use adequate dosage of penicillin or to continue treatment for a long enough time.[4,5] The use of penicillin in rheumatoid arthritis is suggested by the hypothesis that this disease may be due to infection with a penicillin-sensitive organism. The hemolytic streptococcus, Group A, has been implicated on immunologic grounds because a positive streptococcus agglutination reaction occurs in the majority of patients with rheumatoid arthritis.[6] However, the specificity of the reaction has not been established.[7] This evidence has been supported to a slight extent by the demonstration, in agglutinating sera, of precipitins for fractions of Streptococcus hemolyticus[8] and by an elevation in the antistreptolysin-0 titer of sera from many early cases of rheumatoid arthritis.[9] If any infectious agent is to receive consideration in etiology, most evidence points toward this organism.[10,11]

Some workers have suggested that rheumatoid arthritis may be due not to just one invasion of a bacterial agent but to repeated infections. If this were true, prolonged administration of an antibacterial agent might be effective when treatment over a short period of time had previously failed. Because of the low incidence of upper respiratory infection and rheumatic diseases in tropical and subtropical regions,[12] it was thought that eliminating or minimizing the respiratory infections these patients so commonly harbor might exert a favorable influence on the course of their illness.

Our purpose has been primarily to determine whether prolonged oral administration of penicillin would alter the course of arthritis; second, to see if the incidence or severity of various upper respiratory infections usually associated with exacerbation of arthritis could be diminished; third, to determine the levels of penicillin obtainable by the oral route and finally to observe what phenomena, if any, might result from large doses of penicillin given over a long period of time.

MATERIALS AND METHODS

Ten patients were selected for treatment. The study was limited to patients with active disease who were capable of following directions and keeping personal records, in whom the diagnosis was definite and who had received little or no other treatment. Six patients had adult rheumatoid arthritis, Two had rheumatoid spondylitis (Marie-Strümpell) and two patients had juvenile rheumatoid arthritis. Each patient was given a daily record sheet on which he recorded the time that penicillin was taken, the amount, any change in symptoms, the occurrence of any illness or infection and any reaction to penicillin.

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* From the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y.

Penicillin (sodium salt) was dispensed in plain, gelatin capsules without buffer, made up so that six capsules equalled 1,000,000 units for the adults and six capsules equalled 500,000 units for the two children. The patient was instructed to empty the contents of one capsule six times a day into 4 to 6 ounces of tap water which was ingested immediately without buffer or antacid. Each of the adults received 1,000,000 units of penicillin daily. One child, K. P., was unable to tolerate the penicillin solution so she was given the unopened gelatin capsule with tap water. For the first two weeks she received 1,000,000 units daily, then this was reduced to 500,000 because the larger amount caused nausea. The other child, F. A., disliked the taste of the aqueous solution so the contents of each capsule were given in 4 ounces of milk, maintaining a daily dose of 500,000 units. No buffering agent, enteric coating or antacid was employed with the drug. It is necessary to give four or five times the intravenous or intramuscular dose of penicillin orally to obtain comparable blood levels.[13–15] For this reason we gave the large amounts recorded.

Many laboratory procedures were carried out including the agglutination test for hemolytic streptococcus,[6] antistreptolysin-0 determinations,[16] blood counts, urinalysis and repeated erythrocyte sedimentation rates.[17] The concentration of penicillin in the blood and the penicillin-sensitivity of organisms isolated from stool and throat cultures were determined by the serial dilution method.[18,19] Stool and throat cultures were taken before, during and following the course of penicillin. Tongue scrapings of patients developing a brown tongue were examined by Dr. Rhoda Benham in the mycology laboratory. Gastric expressions were done to rule out the possibility of gastric anacidity. This was not found in any instance.

Of ten patients, one failed to continue treatment after four weeks. The remainder completed courses of three to six months. The average total amount of penicillin administered to each patient during the course of treatment was 127,900,000 units. This would seem to be an adequate trial of therapy.

RESULTS

Our criteria of clinical improvement were the same as used in previous communications from this clinic,[21] namely, (1) *striking improvement*—marked subjective and objective change in the patient accompanied by a convincing drop in the sedimentation rate. It will be noted that only one patient showed such a response (F. A.) and he has juvenile arthritis of the type in which we have learned to expect a better than average prognosis; (2) *moderate improvement*—a significant change in the patient's condition subjectively and objectively accompanied by a convincing fall in sedimentation rate; (3) *slight improvement*—improvement difficult to define, drop in sedimentation rate; (4) *none*.

The degree of clinical improvement is noted in Table I. When the results in this study are compared with reports of other measures,[22,23] they are not encouraging. (Table I.) A drop in erythrocyte sedimentation rate to normal occurred in only two patients. Only one of these has maintained a low rate during the follow-up period. A definite drop in sedimentation rate occurred in three patients, little change or an actual rise in rate occurred in the five remaining subjects.

There was an apparent decrease in incidence and severity of upper respiratory infections during the course of penicillin therapy but no correlation could be established between the degree of improvement and presence or absence of such infections. Upper respiratory infections of less than one week's duration without systemic effect have been considered mild; those accompanied by a low-grade fever or lasting more than a week have been considered moderate to severe.

In Table II the range of levels of penicillin in units per milliliter and median values is shown. (In the eighth case, penicillin was

administered in gelatin capsules rather than aqueous solution.) Adequate levels have been obtained comparable to those reported with intramuscular or intravenous administration. Our peak levels have been from 0.1 to 1.6 u/ml. These were attained using an aqueous unbuffered solution of penicillin without any protective agent such as an antacid or enteric coating and seem to corroborate the recently published suggestion that gastric acidity is of minor importance in the destruction of orally administered penicillin.[13,14,25,26]

TABLE I
RESULTS OF TREATMENT OF ARTHRITIS WITH ORAL PENICILLIN

Patient	Diagnosis	Duration of Treatment	Incidence of Upper Respiratory Infections	Median Erythrocyte Sedimentation Rate			Improvement
				Before	During	After	
J. P.	Marie-Strümpell spondylitis	14 wk.	mild × 1	44	34	47	slight
A. G.	Marie-Strümpell spondylitis	26 wk.	none	60	58	57	none
F. A.	Juvenile rheumatoid arthritis	28 wk.	mild × 1	44	11	10	striking
K. P.	Juvenile rheumatoid arthritis	26 wk.	moderate × 1 mild × 1	104	82	63	slight
G. B.	Adult rheumatoid arthritis	12 wk.	mild × 1	32	18	52	moderate
M. W.	Adult rheumatoid arthritis	22 wk.	none	41	31	47	slight
G. M.	Adult rheumatoid arthritis	27 wk.	none	92	90	62	none
F. B.	Adult rheumatoid arthritis	28 wk.	mild × 1 rinorrhea × 2	62	59	80	none
W. O.	Adult rheumatoid arthritis	28 wk.	none	54	43	30	slight
H. G.	Adult rheumatoid arthritis	4 wk.	none	42	33	61	none

Various reports of toxic reactions to penicillin have appeared.[27–35] In our series nausea occurred in three patients, it subsided spontaneously in two while treatment was continued and in the third patient, a 60 pound child, it subsided when the dose was reduced from 1,000,000 to 500,000 units daily. Transient diarrhea was noted in four patients and a small localized rash of two days' duration occurred in another. It was not necessary to discontinue treatment in any instance.

An unexpected finding was the appearance of a brown discoloration of the tongues in seven patients. In some instances a furry appearance accompanied the brown color, suggesting the presence of a fungus. The tongue scrapings of six patients were examined by Dr. Rhoda Benham and a monilia was cultured from four of them. Two cultures were identified as Monilia albicans, two others were non-pathogenic monilia. After the brown pigmentation was definite, two patients were told to swallow the capsules intact rather than in solution. In five to ten days the brown color was nearly gone. One patient, a heavy smoker, retained a tinge of brown presumably because of tobacco. All other patients exhibiting a brown tongue showed a disappearance of pigmentation as soon as treatment was stopped. The color induced was probably due to a concentration of colored material from the penicillin used.

The bacteriologic results of this study, a preliminary survey of which has been presented, are being reported in detail elsewhere.[37] Before treatment the predominance of gram-positive organisms in the throats of all patients except one was indicated by smears and cultures. In most instances colonies of Streptococcus viridans were predominant. Other gram-positive organisms appeared intermittently in some patients prior to therapy. During penicillin therapy throat smears and cultures indicated a predominance of gram-negative forms similar to

those observed occasionally in pre-penicillin cultures, and coliform bacteria which appeared first a short time after beginning therapy. Penicillin-sensitive organisms, including pneumococci and hemolytic streptococci, group A, disappeared from the throats. Examination of stool specimens has indicated a definite inhibitory effect on the gram-positive diplococci of the intestinal tract.

No effect was observed on the anti-streptolysin-0 or streptococcus agglutination titers following penicillin therapy.

TABLE II

PENICILLIN CONCENTRATION IN SERUM OF TEN PATIENTS RECEIVING 500,000 TO 1,000,000 UNITS DAILY IN AQUEOUS SOLUTION

Case	Single Dose* (Units)	Interval between Dose and Bleeding	Unit Penicillin per ml. Serum	
			Range	Median
F. A.	83,000	30 min.	0.05 – 0.4	0.2
		1 hr.	0.0125– 0.2	0.2
		2 hr.	<0.0125– 0.0125	<0.0125
		3 hr.	<0.0125–<0.0125	<0.0025
G. B.	166,000	30 min.	0.05 – 0.4	0.2
		1 hr.	0.1 – 0.2	0.15
		2 hr.	0.025 – 0.025	0.025
		3 hr.	<0.0125– 0.025	<0.025
F. B.	166,000	30 min.	0.2 – 0.4	0.2
		1 hr.	0.05 – 0.4	0.2
		2 hr.	0.0125– 0.05	0.05
		3 hr.	0.0125– 0.025	0.025
H. G.	166,000	30 min.	0.4	0.4
		1 hr.	0.1 – 0.1	0.1
		2 hr.	0.0125–	0.0125
		3 hr.	<0.0125	<0.0125
A. G.	166,000	30 min	<0.0125– 0.2	<0.0125
		1 hr.	<0.0125– 0.1	0.0125
		2 hr.	<0.0125– 0.05	<0.0125
		3 hr.	<0.0125– 0.0125	<0.0125
G. M.	166,000	30 min.	<0.0125– 1.6	0.6
		1 hr.	<0.0125– 0.8	0.4
		2 hr.	<0.0125– 0.05	<0.0125
		3 hr.	<0.0125– 0.025	<0.0125
W. O.	166,000	30 min.	0.1 – 0.8	0.4
		1 hr.	0.025 – 0.8	0.2
		2 hr.	0.05 – 0.4	0.1
		3 hr.	0.025 – 0.2	0.05
K. P.	83,000	30 min.	0.2 – 0.8	0.8
		1 hr.	0.05 – 0.2	0.1
		2 hr.	<0.05 – 0.05	0.025
		3 hr.	<0.0 5 – 0.025	<0.0125
J. P.	166,000	30 min.	<0.0125– 0.1	0.025
		1 hr.	<0.0125– 0.1	0.0125
		2 hr.	<0.0125– 0.025	<0.0125
		3 hr.	<0.0125– 0.0125	<0.0125
M. W.	166,000	30 min.	<0.0125– 0.4	0.05
		1 hr.	<0.0125– 0.1	0.05
		2 hr.	<0.0125– 0.025	<0.0125
		3 hr.	<0.0125– 0.0125	<0.0125

* This dose was repeated six times daily.

COMMENTS

In studying the results with penicillin therapy it should be borne in mind that from 50 to 70 per cent of arthritics will exhibit some degree of improvement with only general supportive treatment.[20] Using various empirical remedies even better results are reported, and in recent years many observers have believed that chrysotherapy was of definite benefit in a large percentage of cases.[38] Aside from the effects on arthritis, there was a diminution in severity and frequency of upper respiratory infections noticed by all of the patients. These infections may vary so much from year to year in any one patient, however, that it would be difficult to assign great importance to this observation.

Penicillin levels of 0.05 u/ml. are effective against most pneumococci, streptococci and other oral pathogens, but not against organisms requiring more than 0.05 unit for inhibition of growth *in vitro*. One report has suggested that effective blood levels during the usual intramuscular doses range from 0.02 to 0.16 u/ml.[24] Peak levels obtained in this work were usually much higher than this. Usually higher levels with a given dose of penicillin are obtained if the drug is taken more than one-half hour before[25] or two hours after meals. With such a schedule only minor variations from the median should appear. Actually, it is impossible to control the exact time of administration in ambulatory patients so that the fluctuations have occasionally been greater as noted in Table II.

A striking observation, considering the length of time and large amounts of penicillin involved in this study, was the paucity of toxic reactions. Mild reactions did occur but it was never necessary to stop treatment because of them. In fact all of the various reactions listed previously disappeared in a day or so as treatment continued.

In a study of one hundred normal throat cultures Dr. Benham isolated M. albicans

from 18 per cent,[36] thus it is impossible to draw conclusions from our small series. No correlation has been established between this phenomenon and penicillin levels but it was observed that patient A. G., who has seldom had high levels when tested, developed a brown, shaggy tongue on the fifth day of treatment, earlier than any other patient.

SUMMARY AND CONCLUSIONS

1. Penicillin has been given by the oral route to ten patients with arthritis. Two patients were moderately to markedly improved, four patients were slightly improved and four patients were unimproved during the course of this study.

2. There seemed to be a diminution in incidence and severity of upper respiratory infections.

3. With one exception, therapeutic levels of penicillin were attained in the serum by oral administration even though no antacid, buffer, enteric coating or other protection was employed.

4. Transient reactions consisting of nausea or diarrhea were observed in five instances. One patient had a two-day rash localized to one leg, probably not associated with penicillin. In no case was it necessary to stop treatment because of persisting reactions.

5. Seven patients developed a brownish discoloration of the tongue while receiving penicillin. Fungus cultures were obtained from six patients, two were positive for M. albicans, two had non-pathogenic monilia and two were negative.

6. Oral penicillin was effective against susceptible organisms when the dosage was increased to four or five times the usual intramuscular dose.

7. Bacteriologic studies demonstrated a change in the predominant organisms of the throat from gram-positive to gram-negative, the disappearance from the throat of penicillin-sensitive organisms, the appearance of coliform bacteria in the throat and a decrease in the prevalence of gram-positive diplococci in the intestinal tract.

8. Antistreptolysin and streptococcus agglutination titers were unchanged with penicillin therapy.

9. Penicillin is not recommended for the treatment of rheumatoid arthritis.

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Oral Penicillin in the Treatment of Various Bacterial Infections*

JAY A. ROBINSON, M.D., HAROLD L. HIRSH, M.D. *and* HARRY F. DOWLING, M.D.
Washington, D. C.

ORAL administration of a drug is the method of choice from the standpoint of the patient's comfort and physician's convenience. In the early studies of the absorption of small doses of penicillin from the gastrointestinal tract only low concentrations were demonstrated in the serum although higher concentrations were obtained in patients with achlorhydria.[1,2] From these observations, plus the fact that penicillin was destroyed in an acid medium, the hypothesis was entertained that low serum levels following oral administration were the result of destruction by gastric juice.[1–4] Many investigators combined penicillin with various protectives in an effort to decrease this destructive action.[5a,26] Further studies of the absorption of large doses of penicillin in aqueous solution given orally demonstrated that the serum concentrations were as good as those obtained with the use of protectives.[2,27] These variable results stimulated several investigators to review the problem of oral administration of penicillin.

McDermott and his collaborators[28] found that at a pH of 2 penicillin was destroyed rapidly and completely; at pH 4 the destruction was slow and incomplete and at pH 7.2 to 7.5 no destruction occurred. They further demonstrated that in normal subjects the pH of the gastric juice was frequently 4 or above, and concluded that the destruction of penicillin in the stomach accounted for only a small fraction (10 to 15 per cent) of the ingested dose. Free and his associates[29] also found that if large doses were given orally, most of the penicillin escaped the action of the gastric juice and that the amount available for absorption through the duodenum was sufficient to produce significant serum concentrations.

Several investigators[28,30,31] recently studied the absorption and destruction of penicillin in various parts of the gastrointestinal tract. They found that the maximal amount of penicillin absorbed from the duodenum was approximately one-third of the amount present, and that destruction of the drug did not occur. Their explanation for the fact that only small amounts were absorbed was that passage through this organ was too rapid to permit complete absorption.

Approximately one-fifth of the amount which reached the jejunum and ileum was absorbed while nearly one-half of the penicillin present in this region was destroyed. Of the amount which reached the colon, only 5 per cent was absorbed while about four-fifths was destroyed. These investigators believed that the destruction in the intestinal tract was due mainly to penicillinase produced by some of the bacteria. An average of 2 per cent of the ingested dose was excreted in the feces. These data indicated that the relative inefficiency of oral dosage was due to the incomplete absorption in the upper intestinal tract and destruction in the lower portions. Furthermore, the effect of protective substances was negligible in comparison with the other factors involved.

In view of the fact that oral administration of penicillin is followed by therapeutically effective concentrations of the antibiotic

* From the George Washington University and Georgetown University Medical Divisions, Gallinger Municipal Hospital, and the Departments of Medicine, George Washington University School of Medicine and Georgetown University School of Medicine, Washington, D. C.

in the serum when sufficiently large doses are given, we decided to employ this route in the treatment of certain diseases.* In general, we selected a dose five times as high as that which we were accustomed to administer intramuscularly for the same diseases.

TABLE I
RESULTS OF ORAL PENICILLIN THERAPY IN VARIOUS INFECTIONS

Disease	Recovered	Unimproved	Died	Dosage-Schedule
Pneumococcic pneumonia	109	...	4	75,000 units every 3 hr. until afebrile for 48 to 72 hr.
Scarlet fever	94	..	0	125,000 units every 3 hr. for 5 days
Tonsillitis and pharyngitis	38	0	..	100,000 to 125,000 units every 3 hr. for 5 days
Erysipelas	6	..	0	100,000 to 125,000 units every 3 hr. for 5 days
Otitis media	16	1	..	100,000 to 125,000 units every 3 hr. for 48 hr. after all evidence of active infection have disappeared
Vincent's angina	6	0	..	50,000 to 75,000 units every 2 to 3 hr. for 3 to 4 days
Infections of the skin	21	1	..	125,000 units every 3 hr. for 5 days
Bacterial endocarditis	0	2	..	Oral penicillin not recommended
Total	290	4	4	

RESULTS

The dosage schedules and the results of treatment in 298 patients with various infections treated with oral penicillin are listed in Table I.

Pneumococcic Pneumonia. Included in the series are 113 patients with pneumonia. No selection was practiced. All patients diagnosed as having pneumonia during the times when oral preparations were available were treated by the oral route. Sputum specimens and blood cultures were obtained before therapy was begun. As shown in Table II a penumococcus was typed from the sputum of ninety-one patients. In the twenty-two patients in whom a pneumococcus was not found the presumptive diagnosis of pneumococcic pneumonia was made on the basis of a typical history, characteristic physical and x-ray findings and leukocytosis. Nine patients had positive blood cultures. Forty-four (39 per cent) of the patients were over forty years of age. (Table III). Lobar pneumonia was diagnosed in ninety-eight patients and bronchopneumonia in fifteen. Twenty patients had involvement of more than one lobe. Among the eighty-eight patients for whom the day of onset could be definitely established, penicillin treatment was begun on the first two days of the disease in 39 per cent of

TABLE II
PATIENTS WITH PNEUMONIA—ARRANGED ACCORDING TO PNEUMOCOCCUS TYPES

Type of Pneumococcus	All Cases		Bacteremic Cases	
	No.	Died	No.	Died
1	10	1	2	1
2	12	0	1	0
3	11	0	0	0
4	6	0	2	0
5	1	0	0	0
6	5	0	0	0
7	13	1	2	0
8	6	0	1	0
Other types	27	1	1	1
No type obtained	22	1	0	0
Total	113	4 (3.5%)	9	2 (22%)

TABLE III
PATIENTS WITH PNEUMONIA—ARRANGED ACCORDING TO AGE

Age Group	No.	Died
12–20	10	0
21–30	26	0
31–40	33	2
41–50	20	0
51–60	12	1
61–70	7	0
over 70	5	1
Total	113	4

*The penicillin used was in the form of tablets buffered with calcium carbonate and was supplied by the Lederle Laboratories, Inc., Pearl River, N. Y.

cases; on the third or fourth days in 31 per cent; on the fifth to the seventh days, inclusive, in 25 per cent and after the seventh day in 5 per cent. None of the patients had received sulfonamides or antibiotics before admission to the hospital.

The dose of penicillin employed in most instances was 75,000 units every three hours, day and night, until the patient's temperature fell and remained below 100°F. for forty-eight to seventy-two hours. Fifteen patients were given 80,000 units and two received 100,000 units every three hours. The larger doses were given without regard to the severity of the disease but because preparations of penicillin were available which made such a dosage regimen convenient.

The results of oral penicillin therapy were comparable with those obtained by intramuscular doses approximately one-fifth as great.

Some of the cases reported herein were included in a previous study[5b] which showed that the case fatality rates, the speed of temperature fall and incidence of complications were comparable with the results in patients treated by the oral and by the intramuscular route, providing the oral dose was five times as great as the intramuscular.

Death occurred in four (3.5 per cent) of the 113 patients in whom oral treatment was employed. Two of the patients were in the age group of thirty-one to forty years. Both had overwhelming infections accompanied by bacteremia and were moribund on admission. One was admitted on the fifth day of illness and the other on the seventh day. Both patients died soon after treatment was started, one patient eight hours and the other fifteen hours after the first dose of penicillin.

The patient aged fifty-four who died was admitted to the hospital on the seventh day of his illness. He died thirty-nine hours after treatment was started and at autopsy was found to have bronchopneumonia throughout the right lung and in the left lower lobe and a fibrinous pericarditis.

The fourth fatality occurred in a ninety-eight year old colored female who recovered from pneumonia and died ten days later from a hemorrhage of the intestinal tract, the cause of which was unknown. Autopsy was not obtained.

Our results with oral penicillin were similar to those obtained by others,[20,21,32] some of whom employed smaller, and others larger doses.

Infections Caused by Beta Hemolytic Streptococci. The pronounced susceptibility of the beta hemolytic streptococcus to the bactericidal action of penicillin stimulated us to treat scarlet fever with this antibiotic. We have given penicillin orally in doses of 125,000 units every three hours for five days to thirty patients, and 100,000 units every four hours for the same period of time to sixty-four patients. The results with oral administration in these doses were comparable to those obtained in eighty-six patients treated by parenteral injections of 25,000 units every three hours for five days.[33] The penicillin caused a prompt fall in temperature, a decrease in toxicity and a pronounced reduction in the incidence of pyogenic complications and the carrier state. Furthermore, in all patients from whose throat a hemolytic streptococcus was cultured, the causative organism disappeared within forty-eight hours and did not reappear while the patient was under observation. The need for antitoxin is apparently obviated except in severely toxic patients or in those who show no response to penicillin after an adequate trial for forty-eight to seventy-two hours. Since penicillin therapy decreases the number and severity of complications, we believe that even the patients with mild cases should have the benefit of the antibiotic. On admission several patients had pyogenic complications such as otitis media, sinusitis and infected wounds. All of these complications responded promptly to penicillin therapy. A more detailed report on the treatment of scarlet fever with penicillin has been published elsewhere.[33]

Patients with streptococcic infections of the pharynx without rash, treated with peni-

cillin orally in doses of 100,000 units to 125,000 units every three or four hours for five days, responded as well as those with scarlet fever. Hemolytic streptococci disappeared promptly from the throat cultures and the symptoms regressed rapidly. The patients appeared well in about seventy-two hours. The results in these thirty-eight patients are comparable to those obtained in thirty patients treated by us with parenteral penicillin.[34] Penicillin treatment should be continued for a minimum of five days; otherwise the incidence of complications and recurrence is high and the complications may be severe.[35] Others have reported similar results.[32,36]

Although the sulfonamides have been highly effective in the treatment of erysipelas, we believe that penicillin is the drug of choice. The six patients treated with 125,000 units of penicillin orally every three hours recovered in five days although the amount of skin involved covered as much as three-fourths of the face in some instances. Within twenty-four hours of the beginning of therapy the lesion stopped spreading. Thereafter, there was prompt regression of all symptoms as well as of the area of involvement so that within an average of five days the skin appeared essentially normal. These results were similar to those obtained in four patients whom we treated parenterally.[34]

Acute Otitis Media. The micro-organisms which affect the middle ear are usually amenable to penicillin therapy. We have treated seventeen such infections with oral penicillin. The results were similar to those observed in fifteen patients treated with penicillin parenterally.[34] The dosage schedule employed was 100,000 to 125,000 units every three hours and this was continued for forty-eight hours after all evidence of active infection had disappeared. Ten patients had acute catarrhal otitis media and seven had a suppurative process. Cultures of the pus in the latter patients yielded beta hemolytic streptococcus in five cases, Staphylococcus aureus in one case and pneumococcus, Type III, in another case. In nine patients the otitis media was apparently a primary infection while in seven patients the ear involvement followed an acute upper respiratory infection. One patient also had Type III pneumococcic pneumonia. Not included in the tabulations are an additional seven patients with scarlet fever who had catarrhal otitis media which was present on admission and which responded to the penicillin administered for the scarlet fever. The patients with acute catarrhal otitis media showed regression of the abnormal findings within twenty-four hours. All signs were usually gone by the third or fourth day. In all of the patients with suppurative otitis media the drainage became thinner and less in amount within twenty-four hours and stopped completely within seventy-two hours. Regardless of the kind of pathologic condition present, the treatment was continued for forty-eight hours after all evidence of active infection had disappeared. Average duration of treatment was seven days. Myringotomy was avoided in all patients except one who had an acute catarrhal otitis media. In this patient the myringotomy was performed after the patient had made a favorable response and the operation may not have been necessary. The one patient who failed to respond had an acute catarrhal otitis media. After there was no improvement following seventy-two hours of oral penicillin therapy the patient was given 25,000 units of aqueous penicillin intramuscularly every three hours for five days with only slight improvement. Recovery finally occurred after seven days of sulfadiazine therapy. Gyorgy and his associates[32] and Lierle and his co-workers[36] have reported results similar to ours with the use of oral penicillin in the treatment of otitis media.

Vincent's Stomatitis and Pharyngitis. The effectiveness of penicillin in Vincent's stomatitis and pharyngitis has been demonstrated whether the antibiotic is administered orally,[36] parenterally[37,43,44] or is employed locally.[38,43,45,48] Our results with oral penicillin in the treatment of six patients with Vincent's stomatitis and pharyngitis were

excellent. Doses of 50,000 to 75,000 units were given every two to three hours for three to four days. Vincent's organisms disappeared within twenty-four hours after the start of therapy, and the symptoms subsided and the lesions disappeared within several days. Although the results with oral therapy were as good as those obtained in six patients treated with intramuscular injections,[34] treatment by the latter method has the advantage that 15,000 to 25,000 units given intramuscularly every three hours for one day will control most infections and only a few patients will require two to four days of treatment.

Infections of the Skin and Subcutaneous Tissues. Prompt recovery occurred in twenty-one of twenty-two patients with various infections of the skin and subcutaneous tissues, including abscesses, cellulitis, carbuncles and impetigo. These patients were given 125,000 units orally every three hours for five days. In all instances the lesions showed evidence of prompt regression with complete resolution of the infections by the time therapy was discontinued. Others have reported similar experiences.[20,32] Our results were comparable to those which we obtained in nineteen patients to whom we[34] gave penicillin parenterally. The one failure occurred in a patient who developed an abscess following an injection of protamine zinc insulin. Healing did not occur until incision and drainage were performed. The pus at that time was cultured and was found to be sterile.

Bacterial Endocarditis. Treatment with parenteral penicillin has revolutionized the prognosis of bacterial endocarditis. Successful use of oral penicillin in the treatment of this infection has been reported.[49] We started treatment of two patients with the administration of penicillin by mouth in doses of 100,000 to 200,000 units every three hours. When there was no clinical improvement and the blood cultures continued to be positive after two days of oral penicillin, intramuscular therapy was substituted. This was followed by prompt control of the infection. In the case of one patient the sensitivity of the Streptococcus viridans was found to be 0.039 units of penicillin/cc. The concentration of penicillin in the serum was determined at regular intervals and frequently found to be below the desired level for the causative organism. Inasmuch as bacterial endocarditis is a serious disease in which penicillin therapy may sometimes fail even under what appear to be the most favorable circumstances and since parenteral therapy in our hands[50] as well as elsewhere now results in cures in about 75 per cent of these patients, we believe that oral therapy should not be employed.

Gonorrhea. We have not treated any patients with gonorrhea by the oral route. Meads and Finland[51] reviewed the cases of 225 patients given oral penicillin. They reported that a favorable response occurred in 190 (85 per cent) of the patients. The dose of penicillin ranged from 100,000 to 1,600,000 units given over a period of one to sixty-nine hours. They concluded that in order to achieve results comparable with those obtained with 75,000 units or more intramuscularly, it is probably necessary to use a total oral dose of 600,000 units or more. Others[52] have had similar results with 600,000 units over a period of seven hours. One investigator[53] reported cures in 92.7 per cent of his patients using 200,000 units given twice over an eight-hour interval.

TOXIC REACTIONS

A number of patients with other diseases were given oral penicillin, making a total of 350 patients who were treated by this route. Among these, eight had toxic reactions. One patient was given two courses of oral penicillin and developed nausea and vomiting immediately after taking each dose of the first course. She had no reaction during the second course. Six patients complained of mild diarrhea which was present only during penicillin therapy and which did not interfere with treatment. No other cause for the diarrhea was found. The eighth patient developed urticaria and pruritus on the third day of treatment. She

was also receiving aspirin and codeine sulfate. The symptoms were relieved by benadryl given orally. Treatment with penicillin was continued for an additional two days. After the completion of therapy she was given test doses of aspirin, codeine sulfate and penicillin without developing a reaction to any of them.

It is quite likely that the nausea, vomiting and diarrhea were due to mechanical factors from the number of tablets that were taken rather than to hypersensitivity to penicillin. When allergic manifestations alone are considered, the incidence of toxic reactions due to oral penicillin is much less than that observed by us in patients treated with the antibiotic given parenterally. Urticaria or fever developed in seven of the 600 patients to whom we gave penicillin intramuscularly or intravenously.

COMMENTS

Simplicity of the oral administration of penicillin makes it one of the more desirable methods of administration of this antibiotic. Because the serum concentration of penicillin is irregular and generally low after this method of administration, it would seem inadvisable to use it in severe infections, in infections in which the causative micro-organisms are relatively resistant to penicillin or in infections in which the penicillin does not have easy access to the bacteria. The wisest procedure is to evaluate the usefulness of oral penicillin by extensive clinical trial in the various diseases in which it might, theoretically, be effective before recommending its use. Preferably, such studies should be controlled by the treatment of similar patients with comparable doses of penicillin administered parenterally.

We have used the oral method to treat 298 patients, most of whom were suffering from infections which were either mild or were caused by bacteria which were relatively susceptible to penicillin. Numerous patients with the same diseases have been treated by us with parenteral penicillin. Usually about one-fifth as much penicillin was used by injection as was administered orally. In some instances alternate patients were given oral and parenteral penicillin. In others the route of administration depended upon the preparation available at the time. In no case was the selection of the route based upon the severity of the disease.

In the case of patients with pneumococcic pneumonia, streptococcic sore throat with rash (scarlet fever), streptococcic sore throat without rash, erysipelas, otitis media, acute sinusitis and certain infections of the skin and subcutaneous tissues, there was no difference between the response obtained when penicillin was administered parenterally and when it was given orally in doses approximately five times as great. It will be noted that these infections were all caused by organisms which are usually inhibited by concentrations of penicillin sufficiently low to be obtainable in the serum when penicillin is given orally in doses of 75,000 to 125,000 units every three hours. On the other hand, oral therapy was not successful in two cases of bacterial endocarditis caused by Str. viridans. This result might be expected in view of the fact that these organisms are sometimes relatively resistant to penicillin and the lesions are not easily accessible to penicillin.[54]

SUMMARY

1. Penicillin was administered by the oral route to 350 patients, and the results were compared with those obtained in over 600 patients treated by intermittent intramuscular injections. The oral doses were approximately five times as great as the parenteral doses.

2. The results were comparable to those obtained with parenteral therapy in the case of pneumonia, streptococcic sore throat, scarlet fever, erysipelas and otitis media. They were less satisfactory in Vincent's stomatitis and poor in the case of bacterial endocarditis.

3. Hypersensitivity reactions were less frequent than with penicillin administered by the other commonly used routes.

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Review

Hypertension and Urologic Disease*

HOMER W. SMITH, SC.D.
New York, New York

NUMEROUS investigators in this country and abroad continue to study animals rendered hypertensive by interference with the renal blood flow, i.e., by one variation or another of the Goldblatt experiment. This experiment is among the classics of modern physiology and has evoked perhaps greater interest and a larger series of publications than any other single experiment of the last two decades. This is wholly appropriate and is to be expected in view of the great importance of hypertensive disease which affects one quarter or better of the adult population. The literature on experimental hypertension runs to well over a thousand papers. It has recently been summarized by several workers in that field[22,46,49] and it is unnecessary to comment on it except in one or two details. Renin, presumed to be the precursor of the pressor substance in the initial stages of experimental hypertension, is demonstrable in the systemic blood for a short time following clamping of the renal arteries in dogs and also in man in circumstances where the renal blood flow is abruptly and markedly reduced; but in dogs with chronic hypertension, as well as in patients with essential hypertension, the most reliable results have been uniformly negative up to this time. If the renin mechanism is solely responsible for the rise in blood pressure in the early stages of the Goldblatt experiment, or in early renal hypertension in man, some other mechanism, apparently quite independent of the renin mechanism, is responsible in the chronic stages in both types. There is, therefore, no warrant to conclude that renin is the pressor factor in well established hypertensive disease, and we remain without any experimental interpretation of the chronic process in man. Nor is it yet demonstrated that the renin mechanism is responsible for early essential hypertension in man.

It was once thought that a unilateral Goldblatt kidney could activate a mechanism in the contralateral, unclamped kidney to produce hypertensive disease but it is now contended that this result is peculiar to the rat. It is very rare for a unilateral Goldblatt kidney to produce a substantial and sustained rise in pressure in the dog; the rise of pressure is at best only moderate and transient. There is therefore no warrant from experiments on dogs for assuming that unilateral renal disease in man can initiate chronic or self-propagating hypertension.

There is a considerable amount of literature on the renal blood flow in essential hypertension and in other pathologic processes in man, and nothing in these data points convincingly to the primacy of renal ischemia. The available data can be equally well interpreted in terms of a disease which produces afferent arteriolar sclerosis as well as functional constriction of the efferent glomerular arterioles (possibly by a humoral mechanism) and to which the kidneys become an easy victim possibly for no other reason than because they receive so large a fraction (approximately one-fifth) of the total cardiac output.

If we assume that hypertensive disease is the result of a multitude of microscopic

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Goldblatt clamps placed upon the renal arterioles in consequence of arteriolar sclerosis, then we must recognize that the arteriolar disease, which itself remains unexplained, is the primary event and there is no reason to limit this to the kidneys. As I have said before,[113] it does not advance our problem and it is illogical to suppose that at one moment humoral agents are operating to reduce renal blood flow and then at the next moment suppose that the reduction in renal blood flow is the reason for the appearance of these agents in the blood.

Alternatively, there are those who argue that renal ischemia or some other disturbance in the renal circulation is brought about by neurogenic constriction of the renal arterioles mediated through the sympathetic nervous system. They imply, as yet without warrant, that the stresses of modern life initiate the hypertensive process along the lines of the Goldblatt experiment by functional vasoconstriction. It has been well demonstrated that severe alarm, pain close to the threshold of toleration and, more recently, neurotic conflict when abruptly precipated[89,110,111,123] can cause renal vasoconstriction in man, although it is not known how much of this vasoconstriction is attributable to neurogenic action and how much to the secretion of adrenalin. However, the surgeons report no success in reduction of blood pressure in hypertensive subjects by renal denervation; in order to achieve any significant reduction in pressure they must destroy almost all the sympathetic nervous system, the primary mechanism by which vasoconstrictor impulses are delivered to the arterioles throughout the body, and even here they are successful no more than about one-third of the time. In the absence of better evidence in favor of the functional vasoconstriction hypothesis and in the face of the stubborn chronicity of established hypertensive disease despite extensive destruction of the sympathetic nervous system, this hypothesis is at best a long guess.

The cause of essential hypertension is as yet unknown. I have previously drawn an analogy with diabetes mellitus.[113] Had someone placed a clamp on the pancreatic artery before the days of Minkowski and obtained diabetes, he might well have been led to the theory that all diabetes is due to pancreatic ischemia or some other disturbance in the pancreatic circulation. This is, of course, not true; it is probably a very rare case in which the pancreatic circulation plays any part; in some instances diabetes possibly can be attributed to a congenital deficiency of islet tissue, in some cases to pituitary dysfunction and in some cases possibly to a disturbance in the adrenal cortex. In the light of our present knowledge it is reasonable to believe that essential hypertension may also have several causes, or in other respects be as complex as diabetes.

The use of thoracicolumbar sympathectomy as a therapeutic measure is one of great interest to both internists and surgeons. I hesitate to cite statistics on so-called successes in sympathectomy because the statistics published by different investigators vary so widely. I have no hesitancy, however, in pointing out that sympathectomy deprives the body of an important mechanism for maintaining blood pressure and it is not as surprising that the pressure falls in some instances as that it should fail to fall in so many others. This failure points to widespread functional changes in the arteriolar bed throughout the body. No evidence has yet been presented that sympathectomy changes the temporal progress of the disease; perhaps some patients will live longer if the danger of cerebral accidents is reduced by lowering the pressure, but the danger of cerebral thrombosis and coronary thrombosis may possibly be increased. One of my colleagues has replied to the question, "When would you recommend sympathectomy in hypertension?" with the answer, "In desperation and experimentation." In the last sense it is unquestionably valuable, but we must await data on the life history of the experimental subjects before considering the experiment complete.

Lastly, I must remark on the unreliability

of the blood pressure itself. Every student of this problem recognizes the lability of pathologically increased blood pressure. A single reading is virtually worthless since blood pressure can be raised or lowered by a variety of unrelated factors. It is the practice among those who are interested in hypertensive disease to hospitalize the patient for two to four weeks and to make repeated blood pressure observations throughout the day before drawing a base line. A large proportion of hypertensive subjects will show a marked reduction in blood pressure, frequently to normal values, under conditions of hospitalization and bed rest. Only after obtaining a long drawn, careful base line may one attribute a reduction of blood pressure to any therapeutic measure. In recent studies in which hospitalized patients were maintained on a fairly standard regimen we have observed that as long as the research nurse took the pressure of certain patients it remained low, but let a physician, even one known to the patient, be in attendance and the pressure might soar to astonishing heights. Conversely, in some instances the nurse proved to be the pressogenic agent.

It is well known that in many patients the blood pressure can be materially lowered by psychotherapy,[2,3] by reporting regularly to the clinic, by reduction in weight or other changes in living habits[36] and by disciplined relaxation,[59] although it may remain refractory to many quasi-specific therapeutic agents.[62] Nor can any significance be attached to relief of symptoms. There is a paper by David Ayman[2] published seventeen years ago which is required reading for anyone interested in the therapy of hypertensive disease. Ayman reviewed thirty-five articles dealing with the treatment of hypertension and he pointed out that in practically every article complete or partial symptomatic relief was reported. Seldom was failure mentioned. The majority of papers reported a moderate reduction of blood pressure and a few reported a marked reduction. But it was consistently demonstrated that the degree of symptomatic relief was greater than the reduction of pressure and symptomatic relief was frequently obtained without reduction of pressure. Included in the alleged therapeutic measures were irradiation of the suprarenal region, application of mistletoe, low salt diet, liver extract, radium to the skull, diathermy, corpus luteum, watermelon extract, subtonin, calcium salts plus low protein diet, benzylbenzoate, desencin, thyroid plus potassium permanganate, animasa, rhodan plus calcium plus diuretin, potassium and sodium sulfocyanate, nitroscleran, luminal, theominal, radium water and Nauheim baths.

Ayman himself studied the effects of applying to forty hypertensive patients under ambulatory conditions the systematic therapeutic measure of making a complete history and physical examination and prescribing seriously and enthusiastically ten drops of dilute hydrochloric acid to be taken in one-half glass of water before meals, three times a day. Thirty-three out of the forty patients showed definite improvement ranging from partial to complete relief of symptoms, giving 82 per cent success. Although possibly neurotic, these symptoms are not imaginary: headache, insomnia, nervousness, fatigue, weakness, loss of appetite and dizziness were most commonly relieved, to which was added a general sense of well being. The majority of patients improved after taking the treatment for one week, but a few were not relieved until the therapy had been continued for three weeks. Only three untoward results were encountered: the medicine made one patient so tired that she had to lie down after taking it; in a second patient it was accompanied by generalized pruritus without any objective change in the skin and the third patient, after three days of therapy, was seized with such headache, nausea and vomiting, chilly feelings, weakness, pain and exhaustion that she had to remain in bed for one week. I repeat that Ayman's paper on the treatment of essential hypertension by dilute hydrochloric acid is required reading for all students of this

problem. As Ayman remarks, "Hundreds of articles have appeared on the successful treatment of hypertension by many different methods and drugs, none of which have any specificity. They all have one thing in common: the enthusiastic treatment of a worried patient."

Van Dyke,[116] in discussing the Weapons of Panacea, quotes Trousseau's injunction, "Always use the new drugs while they still have power to heal," and notes that during the period of medical enthusiasm results can be highly successful; as doubts assail the therapist only an occasional patient is benefited; finally, the physician is frankly skeptical and the previously valuable drug becomes virtually worthless. This leads him to remark that even the laity are amused when the cartoonist depicts a druggist holding a vial before a prospective customer and saying, "It has been a wonder drug for over a week now."

In several places in the world primitive medicine men developed the art of trephining the skull with crude instruments. One may hazard the guess that this anatomic approach was initiated by the patient's complaint of headache and, to extend the guess, we may suppose that in some instances the headache was related to hypertension. Judged by the success of the modern medicine man in relieving headache, insomnia, nervousness and other symptoms by non-specific measures, I think we can confidently believe that craniotomy was once equally successful in maintaining the prestige of the profession. In view of the therapeutic usefulness of dilute hydrochloric acid and other non-specific agents, caution is needed in accepting the specificity of such powerful medicines as sympathectomy and nephrectomy. It is rather too bad that we do not have a few living craniotomies for controls.

The fundamental trouble is that we have no method of evaluating the status of hypertensive disease, except in its malignant stage, other than by blood pressure; and blood pressure, even when repeatedly recorded over a protracted period, is a clinical quicksand. For several years workers in my laboratory have devoted themselves to the task of obtaining better and more reliable criteria of cardiovascular disease and as time goes on I have increasing confidence that they have chosen a wise, if distant, goal.

We need not only a more reliable quantitative assessment but earlier recognition in the benign stage. It has been claimed that essential hypertension is an hereditary disorder or at least that a predisposition to hypertension is hereditary. But mammalian genetics, and particularly human genetics, is proving to be more complex than merely the presence or absence of a dominant gene; the same inherited feature may be variously dominant, recessive or sex-linked in different pedigrees; dominance and recessiveness are themselves not absolute and distinct but in different pedigrees the same gene may manifest itself by a sliding scale of values so that, quite apart from a tendency to skip a generation, so-called lack of penetrance, the same genetic character may have very different somatic effects in two different families.[44] At one extreme, hypertension or its predisposition may be hereditary in some such complex manner; at the other extreme, it may reflect the genetic make-up of the individual without being hereditary—a man may by chance draw a genetic-somatic pattern of such a nature that he is no longer able to fit his environment. What is one man's healthy environment may be another man's poison.[112] Moschkowitz[77] has argued that hypertension, along with Graves' disease, peptic ulcer, cardiospasm, manic-depressive psychosis and paranoia are hyperkinetic diseases arising in civilization. Perhaps we are finding that civilization is pathogenic for the normal man.

The psychiatrist, as I have intimated, believes that he, too, has an interest in this problem, and well he may. The art of getting devils out of the head is an ancient and honorable one, as witness the holes in many prehistoric skulls. There are times when I am apprehensive that we are headed for a civil war in medicine between internal medicine, well established on objective

observation and the experimental method, on the one hand, and its younger and more fancy-free sister sciences, psychiatry and psychosomatic medicine, on the other. Should my apprehension become a reality, it may come about that from the smoke and noise of the battle, the charges and countercharges inevitably to be hurled, when the laity may well come to question whether either side knows what it is talking about, the urologist will emerge the hero when he proclaims "Well, I once had a case . . . and I took one kidney out . . . and I cured high blood pressure." It is our task to calculate the probabilities of that happy event.

First, let us consider the incidence of hypertension in the general population. (Table 1.) The criteria of hypertension and the conditions of blood pressure observation have varied so much that data from various clinics are not strictly comparable; moreover, many statistics, for example those collected with life insurance applications, may represent single observations. Unfortunately, one cannot improve the accuracy of inadequate statistics by multiplying their number and these data must be accepted only as approximations.

The figures of Master et al.,[71] representing 14,849 persons, are based in part upon people gainfully employed, in part upon residents in homes for the aged and in part upon hospital patients; except for the absence of data for ages less than forty, they possibly represent the best cross section available for the population in the middle and later age groups. (The authors review the literature on this subject.) No differentiation is made between arteriosclerosis and essential hypertension and failure to make this distinction is characteristic of most of the available data. All investigators have recognized the increasing incidence of hypertension with advancing age, but Master and his colleagues emphasize the surprisingly high incidence in persons over forty years of age. The figures are, of course, larger if the criterion of 140/90 instead of 150/90 is used. They estimate from population statistics that one-half of the male population of the United States and 60 per cent of the female population of forty years of age or over are hypertensive. The data of Robinson and Brucer[101] cannot be presented in a comparable manner because of the use of independent systolic and diastolic criteria, but these authors state that slightly more than 40 per cent of the adult population is actually or incipiently hypertensive.

TABLE 1
INCIDENCE OF HYPERTENSION IN THE GENERAL POPULATION

	Age	Per Cent Hypertensive		
		Male	Female	Both Sexes
Master, Marks and Dack[71]	40–49	25.9	32.0	
14,849 miscellaneous persons	50–59	40.6	53.4	
(150/90 mm. or over)	60–69	56.3	67.7	
	70–79	65.5	73.3	
	40 and over	40.9	50.7	
Robinson and Brucer[101]				
10,883 insurance policy holders, adults only				
(140/90 mm. or more?)	.....	....	....	40.0
Friedman, Moschkowitz and Marrus[42]	30–39	....	....	10.2
1,006 living controls. (Diastolic	40–49	....	....	26.0
100 mm. Hg or over, or diastolic of 90 mm. and systolic 150 mm. or over.)	50–59	....	....	34.0
	60–69	....	....	47.5
	70–79	....	....	51.0
	30–79	....	....	24.7
Braasch, Walters and Hammer[20]	Less than 20	....	....	0
975 clinic registrations	20–29	....	....	2.1
(Systolic 145 mm. or over)	30–39	....	....	8.4
	40–49	....	....	16.4
	50–59	....	....	28.7
	60–69	....	....	47.4
	70 or over	....	....	53.1
	30 and over	....	....	25.0
Shure[109]				
947 random selections from 11,898 autopsy reports	Under 30	21.4	10.0	15.6
	31–40	25.5	30.6	28.1
150/95 mm. or over or cardiac	41–50	39.8	40.2	40.0
hypertrophy)	51–60	33.5	43.1	36.6
	over 60	43.7	42.1	43.1
	All ages			34.9
Oppenheimer, Klemperer and Moschkowitz[84]				
333 cases. Every 15th patient in series of 5,000 coming to autopsy	.....	....	....	24.0
(155/95 mm. or over)				
Baggenstoss and Barker[4]				
100 control necropsies	.....	....	....	29.0
(150/90 or over and cardiac hypertrophy)				
Emerson and Irving[36]				
1,020 employed males, 21 to 78 years	.....	....	....	11.8?
(criteria not given)				

Friedman, Moschkowitz and Marrus[47] give data from 1,006 consecutive patients admitted to the combined surgical services (other than genitourinary service) of the

Mt. Sinai Hospital, excluding patients with severe anemia, high fever or coronary occlusion. Males and females are about equally represented. The data of Braasch, Walters and Hammer[20] are based on 975 consecutive patients taken at random from registrations at the Mayo Clinic. In both series the rising incidence with age is evident. The average figure of 25 per cent is lower than the 40 per cent indicated by the previous two series, largely because of the inclusion of the younger age group, thirty to thirty-nine.

Perhaps it is only a rhetorical question to ask whether or not patients requiring surgical or medical attention are representative of the general population. This question is certainly pertinent to the data of Shure,[109] Oppenheimer, Klemperer and Moschkowitz[84] and Baggenstoss and Barker,[4] which are based upon autopsy records. These represent patients who came to the hospital mortally sick and as such are not truly representative of the general population. Illness, and particularly fever, may actually have reduced the blood pressure in many patients. Aside from this criticism the figures warrant the conservative statement that the incidence of hypertension, quite low before the age of twenty, increases rapidly thereafter until at the age of forty approximately 25 per cent of the general population are hypertensive, this figure increasing to 60 per cent or above in elderly persons.*

I turn now to the incidence of hypertension in patients with urologic disease, as shown in Table II. For ease of discussion the data are arranged by urologic classification rather than by priority of publication.

Rath and Russek,[92] comparing merchant seamen with and without urologic disease (chiefly nephrolithiasis, ureteral lithiasis, hydronephrosis and prostatic hypertrophy,

TABLE II
INCIDENCE OF HYPERTENSION IN PATIENTS WITH UROLOGIC DISEASE

	Per Cent with Hypertension	
	With Urologic Disease	Controls
Rath and Russek[92]	(357)	(654)
Systolic above 145 mm. with diastolic 94 mm. or below		
10 to 49 years	4.36	3.52
50 to 89 years	25.78	32.28
Diastolic above 95 mm.		
10 to 49 years	5.24	5.41
50 to 89 years	17.96	21.75
Sarnoff[103]		
70 with one or both pelves intrarenal	38	
106 with both pelves extrarenal	37	
Stofer and Kline[114]		
38 with one or both pelves intrarenal	37.0	
38 with pelves extrarenal	39.5	
Shrader, Young and Page[108]		
100 pyelographic abnormalities	22.0	
Braasch and Goyanna[17]		
133 nephroptosis	11.8	
Ritter[100]		
28 urologic developmental anomalies	14.2	
24 developmental anomalies, hydronephrosis or stone with or without infection, observed 5 to 10 years; blood pressure normal at first observation	0.0	
Campbell[26]		
173 prostatism	11.0	
Friedman, Moschkowitz and Marrus[42]		
25 hydronephrosis	36.0	
Braasch, Walters and Hammer[20]		
372 hydronephrosis all ages	13.7	
hydronephrosis under 50 years of age	7.7	
577 hydronephrosis with stone	20.9	
Baggenstoss and Barker[4]		
28 hydronephrotic atrophy	25.0	
Oppenheimer, Klemperer and Moschkowitz[84]		
66 unilateral hydronephrosis or pyelonephritis	32.0	
Abeshouse[1]		
4 hydronephrosis, uncomplicated	0.0	
16 hydronephrosis, complicated	18.7	
Braasch and Wood[21]		
70 perinephritis	4.3	
Ellis and Evans[35]		
Renal dwarfism	Rare	
Friedman, Moschkowitz and Marrus[42]		
32 tuberculosis	15.6	

* Emerson and Irving[36] state that among the first 1,020 men applying for "physical fitness service" there were 120 with hypertension, the criteria for which are not stated. No breakdown is given by age and it may be that the low incidence of hypertension is attributable to the preponderant number of young persons; otherwise the data are disparate with those given by other observers.

TABLE II (*Continued*)

	Per Cent with Hypertension	
	With Urologic Disease	Controls
Braasch, Walters and Hammer[20]		
158 tuberculosis	7.6	
Crabtree and Chaset[30]		
23 tuberculosis	4.4	
Abeshouse[1]		
15 tuberculosis	20.0	
Braasch, Walters and Hammer[20]		
111 miscellaneous	18.0	
Friedman, Moschkowitz and Marrus[42]		
7 miscellaneous	0.0	
Abeshouse[1]		
3 traumatic	0.0	
13 miscellaneous	7.6	
Oppenheimer, Klemperer and Moschkowitz[84]		
18 unilateral narrowing of renal artery	83.0	
97 unilateral hypoplasia	23.0	
Baggenstoss and Barker[4]		
13 unilateral hypoplasia	15.3	
Braasch, Walters and Hammer[20]		
164 nephrolithiasis with infection	22.5	
52 nephrolithiasis without infection	5.7	
Shure[109]		
62 nephrolithiasis	53.2	
Friedman, Moschkowitz and Marrus[42]		
60 neoplasms	28.3	
Braasch, Walters and Hammer[20]		
137 adenocarcinomas	27.7	
Crabtree and Chaset[30]		
41 hypernephroma	14.6	
Abeshouse[1]		
24 neoplasms	12.5	
Morlock and Horton[76]		
240 hypernephromas, males	39.2	
88 hypernephromas, females	53.5	
76 males with other renal tumors	40.8	
48 females with other renal tumors	54.2	
Braasch and Jacobson[18]		
180 bilateral pyelonephritis	26.0	20.0
Shure[109]		
224 bilateral pyelonephritis	47.7	
66 unilateral pyelonephritis	33.3	
Entire series of 290 patients:		
Under 30 years of age (controls)	28.0	15.6
31–40 years of age (controls)	33.3	28.1
41–50 years of age (controls)	41.0	40.0
51–60 years of age (controls)	49.0	36.6
Over 60 years of age (controls)	63.0	43.1
All ages	44.4	34.9

no specific breakdown being given), report the same incidence of hypertension in 357 men with uropathologic conditions and 654 controls. Although the authors give a breakdown by decades, it is sufficient to note that the incidence of hypertension is the same in both groups before and after the age of fifty. They state that they are unable to demonstrate an association between urologic disease and hypertension.

TABLE II (*Continued*)

	Per Cent with Hypertension	
	With Urologic Disease	Controls
Pearman, Thompson and Allen[87]		
500 pyelonephritis (unilateral and bilateral)	9.0	
(500 goiter without hyperthyroidism	.....	10.0
(500 gallbladder disease	.....	7.0
Crabtree and Chaset[30]		
76 unilateral pyelonephritis	9.2	
Abeshouse[1]		
9 acute unilateral pyelonephritis	11.1	
9 chronic unilateral pyelonephritis	11.1	
21 pyonephrosis	14.2	
Friedman, Moschkowitz and Marrus[42]		
69 unilateral pyelonephritis	15.8	
Braasch and Jacobson[18]		
119 less than 50 years of age with bilateral pyelonephritis	16.8	
606 controls less than 50 years of age	.....	9.1
61 over 50 years of age with pyelonephritis	44.2	
369 controls over 50 years of age	.....	37.9
Braasch, Walters and Hammer[20]		
43 pyelonephritic atrophy	46.5	
70 pyelonephritis other than atrophic	18.6	
Baggenstoss and Barker[4]		
48 pyelonephritic atrophy	39.6	
8 pyonephrotic atrophy	37.5	
100 controls	.....	29.0

Ravich[95] believed that the intrarenal type of pelvis is regularly associated with hypertension, but this has been questioned by Sarnoff[103] whose data show a lower incidence (38 per cent) in seventy persons with one or

both pelves intrarenal than in 106 persons (47 per cent) with both pelves extrarenal. Sarnoff concludes that there is no correlation between the two conditions. Similarly, Stofer and Kline[114] find the same incidence in a series of thirty-eight patients with unilateral or bilateral intrarenal pelves as in thirty-eight controls with extrarenal pelves, and again conclude that no correlation can be demonstrated.

Shrader, Young and Page[108] report an incidence of hypertension of only 22 per cent in one hundred subjects exhibiting obvious pyelographic abnormalities such as hydronephrosis, ptosis, polycystic disease, lithiasis and congenital anomalies, a figure which they consider to be not above the normal probability. Braasch and Goyanna[17] conclude that nephroptosis is seldom if ever an etiologic factor, while Ritter[100] concludes that hydronephrosis, whether or not complicated by stone or infection, does not lead to hypertension. In a series of twenty-four patients with developmental anomalies (hydronephrosis or lithiasis with or without infection) who were observed for five to ten years, the blood pressure being normal at the first observation, none developed hypertension in this interval although many had recurrent urinary infection or lithiasis. Campbell[26] finds an incidence of 11 per cent of hypertension in 173 patients with prostatic hypertrophy, a figure which is hard to explain when the incidence of hypertension in unselected groups of men old enough to have prostatism should be 50 per cent or better. From the data of Friedman, Moschkowitz and Marrus,[42] Braasch, Walters and Hammer,[20] Baggenstoss and Barker,[4] Oppenheimer, Klemperer and Moschkowitz,[84] and Abeshouse,[1] hydronephrosis does not appear to be a predisposing cause. Braasch and Wood[21] find an incidence of only 4.3 per cent in seventy cases of clinical perinephritis, most of the patients being under fifty years of age, a figure which they state to be less than one-half of that in a random sample of controls in the same age group. Ellis and Evans[35] note that the incidence of hypertension in renal dwarfism is rare. Hypertension had no undue frequency in renal tuberculosis (Friedman, Moschkowitz and Marrus,[42] Braasch, Walters and Hammer,[20] Crabtree and Chaset,[30] or Abeshouse[1]) and in miscellaneous cases reported by Braasch, Walters and Hammer,[20] Friedman, Moschkowitz and Marrus[42] and Abeshouse.[1] Blackman[11] emphasized the high incidence of arteriosclerotic plaques in the renal arteries of a series of fifty cases of hypertension coming to necropsy, and Oppenheimer, Klemperer and Moschkowitz[84] report that of eighteen subjects shown at necropsy to have unilateral narrowing of the renal artery, 83 per cent had hypertension; but the latter authors were led to the conception that hypertension of unknown origin had resulted in general arteriosclerosis and to the accidental deposition of a plaque in a renal artery. Thirteen of the fifteen positive cases also showed arteriosclerosis of the aorta. The pathologic condition of the artery could not be held to be causal to the hypertension. These same investigators and Baggenstoss and Barker,[4] find no correlation between hypertension and unilateral hypoplasia. Braasch, Walters and Hammer[20] find no correlation with nephrolithiasis without infection; the figure is greater when infection is present, but still is not statistically significant. Shure[109] reports 53 per cent of hypertension among sixty-two patients with nephrolithiasis, without commenting on the absence or presence of infection, but 83 per cent of Shure's hypertensive patients were forty years of age and 40 per cent of them were over sixty. The figure 53 per cent is therefore in line with older age groups without specific renal pathologic disease. Renal neoplasms appear to cause no undue incidence of hypertension according to Friedman, Moschkowitz and Marrus,[42] Braasch, Walters and Hammer,[20] Crabtree and Chaset[30] and Abeshouse.[1] Higher figures are reported by Morlock and Horton,[76] but these writers note that by comparison with other renal tumors hypernephroma exhibits no specificity.

Up to this point the evidence is interpreted as negative by nearly all the writers

mentioned: that is, the incidence of hypertension in the urologic conditions enumerated is no greater than, and it frequently is less than, the incidence to be expected by chance as judged by the frequency of the disease in the general population without urologic disease. It is frequently stated that bilateral pyelonephritis is conducive to hypertension, yet the statistics do not bear this out. Braasch and Jacobson[18] report an incidence of 26 per cent in 180 such cases, a figure which is to be compared with 20 per cent in their control series. At one extreme Shure[109] reports 47.7 per cent when the disease is bilateral, but of the hypertensive patients, 64 per cent were over fifty-one years of age and 82 per cent were over forty-one. Compared by decades with Shure's 947 controls or with other controls, there is little indication of specificity. At the other extreme, Pearman, Thompson and Allen[87] report only 9 per cent in a series of 500 cases with no breakdown as between unilateral and bilateral infection, a figure not only surprisingly low but no higher, as the authors note, than in a comparable series of goiter and gallbladder disease. A similarly low incidence in unilateral pyelonephritis is reported by Crabtree and Chaset,[30] Abehouse[1] and Friedman, Moschkowitz and Marrus.[42] Crabtree and Chaset express the view that the pathologic and anatomic elements seem less important in this problem than an as yet unknown physiologic element. Braasch and Jacobson[18] find a greater incidence of hypertension in pyelonephritis than in their own control series, both before and after the age of fifty. Although they are inclined to the belief that chronic bilateral pyelonephritis exercises a definite influence on the incidence of hypertension, especially among patients less than fifty years of age, the indication falls short of proof relative to the other statistics. Braasch, Walters and Hammer[20] and Baggenstoss and Barker[4] record a high incidence of hypertension in unilateral pyelonephritic atrophy and Baggenstoss and Barker[4] in unilateral pyonephrotic atrophy. Both groups of workers lean to the belief that a causal relationship is indicated by these statistics

With these possible exceptions, namely, pyelonephritic and pyonephrotic atrophy, the above data do not indicate that urologic disease increases the incidence of hypertensive disease, or that in any large number of instances it is causally related to its genesis. Hines and Lander[53] report that among 264 patients with urologic disease, who were observed over a period of ten years or more (average 15.3 years), the incidence of hypertension either prior to or subsequent to the first observation was practically identical with a control series of 790 patients without urologic disease. Hines and his co-workers have emphasized the hereditary aspects of hypertensive disease and believe that hereditary factors are more important than any type of renal involvement.

To complete the literature on this subject, I turn briefly to papers dealing with the incidence of urologic abnormalities in otherwise unselected hypertensive patients. (Table III.) The earlier papers of Longcope[70] and of Weiss and Parker,[119] suggesting a significant correlation between pyelonephritis and hypertension, coupled with the rapidly expanding literature on the Goldblatt experiment and Butler's[25] report of reduction of blood pressure by unilateral nephrectomy in an eight year old girl, led investigators to suspect that urologic disease, sometimes of an apparently minor nature, might be the origin of this obscure pathologic process.

In 1941, Schroeder and Steele[105] reported that of 250 living patients with hypertension, 113 or 45 per cent, showed urologic disease of one kind or another. On reviewing their evidence in 1943, however, my colleagues and I noted that fifty-three patients of these 113 positives had bilateral disease, eight had glomerulonephritis, seventeen had bilaterally abnormal pyelograms and there were twenty-eight in whom bilateral renal disease was suspected though not proven, leaving only 60 of 250 or 24 per cent with possible, but unproved, unilateral

disease.[113] Moreover, judgment of urologic fault in Schroeder and Steele's series was based largely upon abnormal radiograms obtained by intravenous or retrograde pyelography, and Chasis and Redish[28] have shown that the pyelogram is a hazardous basis for the diagnosis of abnormality since an innocuous angulation of the ureter or dilatation of the pelvis can give the impression of abnormality, although there is actually no obstruction of the lumen or functional evidence of renal impairment. The significance of many of the residual sixty cases presented by Schroeder and Steele's series is therefore open to some doubt. Wosika, Jung and Maher[124] reported urologic abnormalities in 227 out of 568 necropsies of hypertensive subjects, or an incidence of 40 per cent, a figure to be compared with 27.4 per cent in 611 control necropsies. These authors included all types of unilateral and bilateral disease and their criterion of hypertension rested solely upon the systolic pressure; for these reasons the significance of their calculation is open to question. Hayes and Ashley[51] reported twenty-eight out of fifty-five abnormalities (including meatal stenosis, urethral stricture and urethral angulation) or 51 per cent, but the alleged abnormalities were not such as to be associated invariably with disturbed renal function.

TABLE III
INCIDENCE OF UROLOGIC DISEASE IN HYPERTENSION

	Per Cent with Urologic Disease
Schroeder and Steele[105]	
250 hypertensives, (pyelographic)	45.0
After selection by Smith, Goldring and Chasis	24.0
Wosika, Jung and Maher[124]	
568 necropsies, no selection	40.0
Hayes and Ashley[51]	
55 hypertensives (urographic)	51.0
Flocks[40]	
132 hypertensives (pyelographic)	15.0
Palmer, Chute, Crone and Castleman[85]	
212 hypertensives (pyelographic)	22.0
Sarnoff[103]	
50 hypertensives (one or both intrarenal pelves)	40.0
100 normotensives (one or both intrarenal pelves)	30.0
Hyman and Schlossmann[58]	
55 necropsies 200 pyelograms	no correlation with intrarenal pelves, calculi or hydronephrosis
Shrader, Young and Page[108]	
114 hypertensives (abnormal renal pelves)	19.0
Ratliff and Conger[93]	
188 hypertensives with urinary symptoms (pyelographic)	25.5
340 hypertensives without urinary symptoms (pyelographic)	9.4
Ratliff, Nesbit, Plumb and Bohne[94]	
2,055 hypertensives (pyelographic)	8.9
Bechgaard[8]	
1,038 hypertensives (pyelonephritis and urolithiasis)	7.7
Pearman, Thompson and Allen[87]	
12,000 hypertensives (500 only had urologic examination, the other 11,500 giving no history of renal disease)	3.2
Braasch[16]	
4,000 hypertensives (routine clinical examination	2.5
Lisa, Eckstein and Solomon[69]	
56 hypertensives	caliber of renal arteries same as in 44 controls
Chasis and Redish[27]	
21 hypertensives	no unilateral anomalies or unilateral decrease in function

More moderate estimates are given by Flocks[40] who reported 20 of 132 pyelographic abnormalities, or 15 per cent,* and Palmer, Chute, Crone and Castleman[85] who report 47 of 212 pyelographic abnormalities, or 22 per cent (unilateral in 16 per cent). These figures are less than the 27 per cent incidence reported by Wosika, Jung and Maher in their 611 controls.

Sarnoff[103] reports the presence of one or both intrarenal pelves in 40 per cent in a series of fifty living hypertensives, but he finds an incidence of 30 per cent in one hundred controls and considers that the difference is not significant. Similarly, Hyman and Schlossman[58] report the incidence of intra- and extrarenal pelves in fifty-five autopsied patients who had hypertension. Shrader, Young and Page[108] report the presence of pyelographic abnormalities in 22 out of 114 living hypertensives or 19 per cent and note that it is practically

* Flocks reports reduced phenolsulfonephthalein excretion in 20 of 23 hypertensive patients but this is to be expected in view of the decrease in renal function characteristic of the disease.

difficult to obtain a control series of pyelograms, because such normotensives as are subjected to urologic study generally have urologic abnormalities. They point out, however, that out of one hundred pyelograms exhibiting obvious abnormalities, only 22 per cent of the patients were hypertensives.

Ratliff and Conger[93] found that 25.5 per cent of 188 hypertensive patients who showed urinary symptoms had pyelographic abnormalities, but the incidence of such abnormalities was only 9.4 per cent among 340 hypertensives without urinary symptoms.

Still more conservative are the data of Ratliff, Nesbit, Plumb and Bohne[94] who found an 8.9 per cent incidence of urologic disease in 2,055 hypertensives, of which number 1,350 were examined solely in an effort to determine a possible renal cause for hypertension; of Bechgaard,[8] who found 7.7 per cent cases of pyelonephritis and urolithiasis in 1,038 living hypertensives and of Pearman, Thompson and Allen,[87] who found that among 12,000 patients who had hypertension 500 only gave a history of renal disease such as to lead to intravenous urologic examination; of the total series only 3 per cent had urologic disease. Admittedly, some urologic abnormalities may have been overlooked among those who did not receive urographic study, but such must have been minor affections.

Similar statistics have been reported by Braasch.[16] Among 4,000 hypertensive patients he found clinical evidence of a nonnephritic renal lesion in approximately one hundred, or 2.5 per cent. Hyman and Schlossman[58] record their opinion that there is no correlation between intrarenal pelvis, calculi or hydronephrosis and hypertension, and Lisa, Eckstein and Solomon[69] found the caliber of the renal arteries in fifty-six consecutive hypertensive cases the same as in forty-four controls. In only two instances of the fifty-six did a renal artery show extreme stenosis.

Rath and Russek[92] add together the statistics of Palmer and his co-workers, Ratliff and Conger, Braasch, Schroeder and Steele and others and they note that of a total of 6,044 hypertensive patients, 10.7 per cent exhibit evidence of urologic disease. They contrast this figure to the 27.4 per cent incidence in normotensives reported by Wosika, Jung and Maher and conclude that the incidence of urologic disease among hypertensives is not greater, and possibly less, than among normotensive subjects.

Lastly, Chasis and Redish,[28] in clearance studies of twenty-one hypertensive subjects selected at random, demonstrated that renal functional impairment proceeds to an equal degree or at a parallel rate in both kidneys, a circumstance to be expected if renal injury is a result of the hypertensive process, but not if renal pathologic disease is primary. This evidence has always seemed to me to be the most convincing demonstration that in the majority of instances the kidneys are the victim and not the culprit in this disease.

To conclude on the basis of the above data that perhaps as many as 10 per cent of hypertensive patients have demonstrable urologic abnormalities of such a nature as to lead to functional impairment (and the figure 10 per cent seems generous in view of the data of Ratliff, Bechgaard, Pearman, Braasch and their co-workers), is no warrant for inferring that in these 10 per cent the urologic disease is responsible for the hypertension. The probability of coincidence is very great. At the present time the only way a causal relationship can be demonstrated in any particular case is by curing the hypertension by removing the offending organ. When my colleagues and I reviewed this question four years ago we found that of seventy-six instances of unilateral nephrectomy reported in the literature there were only seven that fulfilled our criteria for a lasting and significant reduction in blood pressure by the removal of the diseased kidney.[113] About six months later Sensenbach[107] published a review which had been prepared without knowledge of our paper. He covered nearly the same literature and concluded that out of a total of seventy-five cases only five fulfilled his criteria for

TABLE IV

SUMMARY OF UNILATERAL NEPHRECTOMIES IN HYPERTENSIVE DISEASE

Author	Effects on Blood Pressure			
	No Significant Reduction	Reduced, But Not to Normal	Reduced to Normal Observation Less Than One Year	Reduced to Normal for One Year or More
Butler[25]	..	..	..	1
Boyd, Holmes and Lewis[14]	..	..	1	
Barney, Dellinger and Suby[6]	..	..	..	1
Bothe[13]	1	1		
Kerr[84]	4	2	..	1
McIntyre[74]	..	..	..	1
Mulholland[80]	1			
Oppenheimer, Klemperer and Moschkowitz[84]	..	1		
Barker and Walters[5]	..	2	3	
Bartels and Leadbetter[7]	..	..	..	1
Crabtree and Chaset[30]	10	..	..	1
Everett[37]	1	3		
Horton[55]	..	..	..	1
Howard, Forbes and Lipscomb[57]	..	..	..	(1)*
Palmer, Chute, Crone, Castleman[85]	8	1		
Patch, Rhea and Codnere[86]	..	..	..	1
Schroeder and Fish[104]	5	2		
Abeshouse[1]†	6	5		
Benjamin and Ratner[9]	1			
Burkland[24]	..	..	..	1
Newbit and Ratliff[82]	4	1	6	
Onell and Munoz[83]	..	..	1	
Richardson and Smart[97]	..	1	1	
Braasch and Wood[21]	2‡			
De Takats, Heyer and Keeton[34]	1	1§	1	
Farrell and Young[38]	..	..	..	1
Friedman, Moschkowitz and Marruss[42]	26	..	..	2
Friedman, Meyer, Selzer, Kreutzmann and Sampson[43]	2	3		
Gibson[45]	..	..	1	
Powers and Murray[90]	..	..	..	1
Ratliff and Conger[93]	3	3	3	
Riskind, and Greene[99]	..	14		
Wilson and Chamberlain[122]	..	..	..	1
Hotchkiss and Gilgrain[56]	1			
Jeck, Hotchkiss and Geary[60]	1			
McMartin and McCurdy[75]	..	3	..	1
Sweeney and Pace[115]	..	..	..	1
Weiss and Chasis[118]	1			
White, Durkee and Mirable[121]	..	..	..	1
Besson[10]	..	..	..	1
Dean and Abels[33]	..	..	..	1
Higbee[52]	..	1	..	1
Leiper[67]	..	..	..	1
Mosenthal[78]	..	..	..	1
Movin, Ohlsen and Pedersen[79]	..	..	..	1
Semens[106]	..	..	..	1
Sensenbach[107]	3	..	..	1
Kennedy, Barker and Walters[63]	..	..	..	1
Perry[38]	..	..	..	2
Wallace[117]	2	1	..	2
Kittredge and Brown[65]	2	2		
Crosbie and Fischmann[32]	11			

(*Table IV concluded on p.* 736)

significant and lasting reduction of blood pressure. Both Sensenbach and ourselves required that the blood pressure be lowered to or below 140/90; we required that it remain within normal limits for at least one year, while Sensenbach required two years.

TABLE IV.—*Continued*

Author	Effects on Blood Pressure			
	No Significant Reduction	Reduced, But Not to Normal	Reduced to Normal, Observation Less Than One Year	Reduced to Normal for One Year or More
Kreutzmann[66]	2			
Ratliff, Nesbit and Plumb and Bohne[94]‖	26	8	..	15
Wattenberg‖	..	1		
Petch‖	1			
Drew‖	..	..	..	1
Langley and Platt‖	10	..	..	1
	135	43	17	47

* Bilateral lumbar sympathectomy, probably chronic diffuse glomerulonephritis.

† Includes five questionably hypertensive individuals.

‡ One incomplete observation.

§ Inadequately reported.

‖ Details on the patients reported by Ratliff et al.[94] are given by Nesbit (*Brooklyn Hosp. J.*, 5: 5, 1947). The writer has excluded by definition two cases (M. S and R. K.) which these authors considered successful.

Since preparation of this manuscript, the writer has seen the papers of Langley and Platt (Langley, G. J. and Platt, R. *Quart. J. Med.*, 16: 143, 1947) who report a successful result in an eight year old child with congenital hypoplastic kidney, and he has received by personal communication from Dr. Edwin J. Drew of New York Hospital the report of a successful operation in the case of an eight year old girl with a pyelonephritic kidney.

Wattenberg (*Ann. Int. Med.*, 25: 734, 1946) reports what we consider a doubtful case, Petch (*Brit. Med. J.*, 4527: 547, 1947) reports one negative case, and Langley and Platt report ten negative cases. These data are included in Tables IV, V and VI.

Movin, Ohlsen and Pedersen[79] cite four cases in Danish literature not immediately available to the writer.

Since that time this literature has expanded and, although several articles contain excellent reviews, it is profitable to bring this topic up to date.*

In Table IV are listed the results of 242 operations recorded† under Sensenbach's four categories: cases which have shown no reduction in blood pressure, cases in which the pressure was reduced but not to normal, cases in which the pressure was reduced to normal but the observation period was for less than one year and cases in which the blood pressure was reduced to normal for one year or longer. This last group constitutes what we may call "cures" of renal hypertension effected by unilateral nephrectomy. There are now on record reasonably well documented accounts of forty-seven such successful cases. Since in reviewing this literature I have made a selection according to certain specified criteria, I have been unable to include several to which only general reference is made. The operation appears to have been successful 19 per cent of the time.

In Table V these forty-seven successful operations are listed, and Table VI gives a summary of pathology. Braasch and his

* Kreutzmann[66] records that he has reviewed every case published up to 1946, and found fifty-four patients in whom the pressure was reduced to below 150/90 for one year or longer. It must be noted, however, that he considers the two subjects reported by him as positive whereas we consider them as negative since the blood pressure remained at 156/94 and 170/100 respectively.

† Movin, Ohlsen and Pedersen[79] cite four additional cases in Danish literature not immediately available to the writer.

TABLE V

RENAL PATHOLOGY IN CASES IN WHICH UNILATERAL NEPHRECTOMY HAS BEEN SUCCESSFUL IN REDUCING BLOOD PRESSURE

Author	Pathology	Age at Operation
Butler[25]	Calculus-pyelonephritis	8
Barney, Dellinger and Suby[6]	Pyelonephritis	10
Kerr[84]	Congenital hypoplasia	16?
McIntyre[74]	Pyelonephritis	36
Bartels and Leadbetter[7]	Hydronephrosis	37
Crabtree and Chaset[30]	Hypernephroma	?
Horton[55]	Hypernephroma	50
Patch, Rhea and Codnere[86]	Pyelonephritis	12
Burkland[24]	Ectopic kidney with arterial occlusion	5½
Farrell and Young[38]	Hematogenous cyst	18
Friedman, Moschkowitz and Marrus[42]	Tuberculosis	?
	Pyelonephritis	?
Powers and Murray[90]	Pyelonephritis	6
Wilson and Chamberlain[122]	Pyelonephritis	12
McMartin and McCurdy[75]	Pyelonephritis	39
Sweeney and Pace[115]	Pyelonephritis	1
White, Durkee and Mirable[121]	Hydronephrosis	39
Besson[10]	Pyelonephritis	34
Dean and Abels[33]	Radiation sclerosis	28
Higbee[52]	Congenital hypoplasia	12
Leiper[67]	Tuberculosis and Atherosclerosis	18
Mosenthal[78]	Atrophic kidney with ureteral occlusion	37
Movin, Ohlsen and Pedersen[79]	Pyelonephritis	6
Semans[106]	Pyelonephritis	2½
Sensenbach[107]	Ureteral occlusion	41
Kennedy, Barker and Walters[63]	Pyelonephritis	7
Perry[88]	Infarct	32
	Infarct	20
Wallace[117]	Pyelonephritis	43
	Pyelonephritis	37
Langley and Platt*	Congenital hypoplasia	8
Drew*	Pyelonephritis	8
Nesbit*	Pyelonephritis	21
	Pyelonephritis	49
	Pyelonephritis	52
	Pyelonephritis	42
	Hypernephroma	56
	Pyonephrosis	13
	Pyonephrosis	60
	Tuberculosis	27
	Pyonephrosis	51
	Pyelonephritis	41
	Hydronephrosis	30
	Hydronephrosis	24
	Hydronephrosis	20
	Pyonephrosis	50
	Pyelonephritis	49
	Total	47 cases

* See Footnote ‖ at end of Table IV.

colleagues have expressed the opinion that among those rare cases suitable for operation the best results are to be expected in unilateral, atrophic pyelonephritis.

In Table VII these operations are listed by age. Although seventeen successes are

TABLE VI
PATHOLOGY IN SUCCESSFUL UNILATERAL NEPHRECTOMY

	No. of Cases
Pyelonephritis	22
Hydronephrosis	5
Pyonephrosis	4
Hypernephroma	3
Tuberculosis	3
Arterial occlusion	1
Hematogenous cyst	1
Ureteral occlusion	2
Infarct	2
Congenital hypoplasia	3
Radiation sclerosis	1
Total	47

reported in persons under twenty years of age, twenty-four were in their fourth or later decade. The rise in the percentage of successes from 9 per cent four years ago to 19 per cent as of this date may merely reflect the fact that as more nephrectomies have been performed, better selection of patients has been made. On the other hand, the fact that unilateral nephrectomy is successful in reducing blood pressure in only 20 per cent and probably fewer of the instances in which it has been tried, is certainly poor proof of any hypothesis. The fact that the hypothesis works only 20 per cent of the time, combined with the astonishing paucity of hypertension in the quoted data on intrarenal pelves, hydronephrosis, tuberculosis and even bilateral pyelonephritis, leaves a lingering doubt that even these forty-seven apparent successes may be fortuitous and failing of demonstration that the urologic disease was actually the cause of hypertension. As Braasch has suggested in the case of pyelonephritis, renal disease may not produce hypertension in an otherwise normal person, but it may serve as an irritant, somatically and psychically, to bring out latent hypertension or cause exacerbation of an otherwise mild process.

TABLE VII
AGE IN SUCCESSFUL UNILATERAL NEPHRECTOMY

Age in Years	No. of Cases
0– 9	9
10–19	8
20–29	6
30–39	9
40–49	6
50–59	5
60–69	1
Not stated	3
Total	47

However, as the evidence stands, we are, I think, obliged tentatively to accept these forty-seven patients as "cured." But it would be a most valuable contribution to this problem if those who have reported reduction of blood pressure by nephrectomy would report, at some date in the near future and perhaps for publication in a single issue of an appropriate journal, follow-up studies on all these patients.

In considering the future of this problem, it is worthwhile to state again our requirements for "successful" unilateral nephrectomy. It must first be demonstrated that the patient is truly hypertensive and not simply showing a transiently elevated blood pressure. Second, elevated blood pressure is so labile and so frequently reduced by bed rest or non-specific therapy that little significance can be attached to partial reduction. It is required that the blood pressure be reduced to normal range, i.e., to or below 140/90 and that it remain at this range long enough to exclude non-specific effects. Abeshouse[1] and Goldring, Chasis and myself[113] required one year, while Braasch[15] and Sensenbach[107] have recommended two years. Perhaps the longer period is the wisest if we are to be certain that we have "cured" the disease.

Braasch[16] estimates that urologic disease is present in no more than 2.5 per cent of hypertensive subjects and that in only one-fifth of these does it present surgical potentialities. This is at best one in 200 persons with hypertension. By rough calculation this would indicate there may be 30,000 persons in the United States who might be aided by unilateral nephrectomy. This is far from therapeutic nihilism and while the internist and psychiatrist settle their differences on the genesis of essential hypertension, the

urologist should search diligently for his potential victories.

But it cannot be emphasized too strongly that, except in rare and well studied instances, the advisability of nephrectomy must rest upon conservative and recognized surgical indications and not upon the hope of reducing blood pressure. In many instances we may expect bilateral renal disease (glomerulonephritis, pyelonephritis, etc.) to be present and it is to be especially noted that hypertensive disease itself is accompanied by a slow, progressive and bilateral destruction of the renal parenchyma,[47,48] a very important point that is generally overlooked in this problem. To remove one kidney which is supplying perhaps 30 to 40 per cent of the total functional renal tissue available to the patient may well shorten his life. With Sensenbach[107] we emphasize that before removal the diseased kidney should be shown to be essentially functionless and the other kidney free of any evidence of disease.

Even under these conditions there is no certainty of success. May I cite a single instance in which detailed data are available. Weiss and Chasis[118] report the results of unilateral nephrectomy in a woman of thirty-four with hypertension of perhaps no more than one and one-half years' duration. Unilateral examination by the clearance methods revealed that the left kidney had negligible glomerular and tubular function, whereas the right kidney showed no evidence of renal disease by the best available methods; on the contrary it was hypertrophic and showed supernormal function in respect to filtration rate, tubular function and blood flow. The left kidney was removed and proved to be an atrophic pyelonephritic kidney weighing 33 Gm. Two months after operation the right kidney was examined again and continued to show supernormal function in respect to filtration rate, blood flow and tubular function. It was practically the equivalent of two normal kidneys. By all criteria this patient was an ideal selection for operation and yet the operation failed to affect her blood pressure in any way. This example illustrates that it is impossible to know in advance whether the operation will or will not be a "success." The best that can be said is that the operation apparently did her no harm, for the kidney that was removed was functionless, while the remaining kidney was good for the work of two. But in how many cases of nephrectomy are these conditions met? Trousseau's admonition to use the new remedy while it still has the power to heal seems to have found its target in this field. Enthusiasm for nephrectomy appears to be on the wane. I regret that from the enthusiastic phase I have been able to cite only forty-seven cases of the "cure" of hypertension by nephrectomy, and that Braasch's estimate, which is perhaps optimistic, indicates that there are only 30,000 possible candidates for surgical treatment in the entire United States. This figure is a trifling one in comparison with the 15,000,000 adults (i.e., those above twenty-five years of age) who are estimated to have hypertensive disease. A short time ago my colleagues and I calculated from data supplied by the Bureau of the Census that about 1,000,000 persons above the age of forty-five die in this country every year; of this number approximately 450,000, or one out of every two, die of one or another sequela of cardiovascular-renal disease, nearly five times as many as die of cancer. A large fraction of cardiovascular-renal disease is hypertensive in origin, presenting us with what is perhaps medicine's major problem. But if we bring to bear upon this small sector of the battle (unilateral renal hypertension) all the attention and acuity at our command, always adhering to the surgeon's ideals of never to risk shortening a patient's life and never to operate in vain, we may not only multiply this modest number of successes but we may help to pave the way to a better understanding of the disease itself.

SUMMARY

The cause of essential hypertension remains unknown. Despite the large amount

of experimental knowledge available from the Goldblatt experiment, it is not yet demonstrated that the human disease has its origin in either pathologic or functional disturbances of the renal circulation. The data can be interpreted equally well in terms of a generalized and perhaps complex pathologic process which, by arteriolar sclerosis and possibly other mechanisms, attacks the renal parenchyma along with other organs. Although sympathectomy lowers the blood pressure in some instances, it is not yet demonstrated that it changes the temporal progress of the disease.

Pathologically elevated blood pressure is well known to be labile in many persons and susceptible to reduction spontaneously and by prolonged bed rest, psychotherapy and many non-specific agents which have in common only the "enthusiastic treatment of a worried patient." Blood pressure is an unreliable guide to the presence or severity of the disease and more reliable criteria are needed.

Statistical data on blood pressure among the general population indicate that the incidence of essential hypertension, quite low before the age of twenty, increases rapidly thereafter until at the age of forty approximately 25 per cent of the general population are affected, this figure increasing to 60 per cent or more in elderly persons.

There is no convincing evidence that this already high incidence of hypertension is increased by urologic disease (nephrolithiasis, hydronephrosis, prostatic hypertrophy, intrarenal pelvis, nephroptosis, perinephritis, congenital aplasia, pyelonephritis), or, conversely, that the incidence of urologic disease is any greater among hypertensives than among normotensives.

At present the only way a causal relationship between urologic disease and hypertension can be demonstrated in any particular patient is by "curing" the hypertension by removing the offending organ. Because of the lability of pathologically elevated blood pressure, rigid criteria must be observed: i.e., clear demonstration of pre-existing hypertension, clear demonstration of reduction of blood pressure to normal levels (140/90 or below) and clear demonstration of persistence of pressure at this level for one year or longer. Review of the literature on unilateral nephrectomy reveals that these criteria have apparently been fulfilled in only forty-seven instances out of 242 reported operations.

These forty-seven instances indicate that unilateral renal pathology may be a cause of hypertension in rare instances but the very rarity of success (19 per cent), coupled with the evidence that the bulk of urologic disease does not cause hypertension, still leaves a reasonable doubt about the hypothesis.

The advisability of nephrectomy must rest upon conservative and recognized surgical indications, and not upon the hope of reducing blood pressure. If bilateral disease is present, and it usually is present in advanced hypertension, as a result of the hypertensive process itself, nephrectomy may shorten life by removing an important fraction of total available renal function.

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Seminars on Hypertension

Surgical Treatment of Hypertension*

R. H. SMITHWICK, M.D.

Boston, Massachusetts

SURGICAL treatment of hypertension has been under investigation in a number of clinics during the past twenty years. The three procedures which may be helpful are extensive sympathectomy, unilateral nephrectomy and the removal of adrenal tumors. Extensive sympathectomy is the most widely applicable procedure.

Hypertension, particularly in its later stages, is a complex disorder in which many factors such as the age and sex of the patient, type and the duration of elevated blood pressure and the degree and location of cardiovascular disease vary greatly. While the cause is unknown, there seems to be rather general agreement that elevated blood pressure is the result of increased peripheral resistance to blood flow through the arterioles. Its onset is insidious and in most patients the blood pressure is unusually variable. There is reason to believe that the disorder passes through several stages. The earliest may consist of an unusually variable blood pressure within a normal range, the so-called normotensive hyperreactor of Hines and Brown.[1,2] As years pass by the basal level rises, but it may still be within the usually accepted normal range under resting conditions. On the other hand, blood pressure is usually elevated under conditions of stress and strain or physical activity. This has been called the stage of intermittent hypertension. This stage appears to be tolerated well by most patients, particularly females. In occasional patients, generally males, cardiovascular damage makes its appearance. After a variable period of time, probably many years, the blood pressure level becomes continually elevated and the upward fluctuations are superimposed. By this time cardiovascular damage is demonstrable in the great majority of patients, in 97 per cent in my experience.[3]

In the earlier stages of the disorder peripheral resistance is increased intermittently. Later, when blood pressure levels are continually elevated, peripheral resistance is always increased but continues to vary in an upward direction. Cardiovascular disease develops along with hypertension and is progressive. The rate of progress is unpredictable and varies from slow to very rapid. It seems probable that vascular disease is to a large measure the result of increased stress and strain upon the blood vessels. The elevated pressure is in all probability due to increased tone of arteriolar smooth muscle. Vascular disease when present is likely to perpetuate the hypertensive process and prevent the reduction of blood pressure after removal of the physiologic causative mechanisms. For instance, hypertension may be caused by an adrenal tumor. In time vascular disease will develop. The vascular changes may be identical with those in patients having so-called "essential" hypertension. If the changes are sufficiently marked and involve a large vascular area, such as the splanchnic bed, removal of the tumor may have no effect upon the blood pressure. The same is true of patients with continued hypertension of the essential variety. The amount and distribution of vascular disease varies tremendously. Following through denervation of the splanchnic bed, the blood pressure levels may be lowered in a striking fashion

* From The Smithwick Foundation, Massachusetts Memorial Hospitals, Boston, Mass.

in the presence of extensive disease of the renal arterioles in one patient and in another there may be no change at all. The presumption is that in the first patient the peripheral resistance was decreased in the extrarenal visceral vascular bed while in the second, because of vascular disease, it was not modified. The alternate possibility is that some additional factor causing increased tone of smooth muscle existed in the second case, such as a humoral substance acting directly upon smooth muscle.

The three factors which appear to affect peripheral resistance in hypertensive patients are nervous, humoral and vascular disease. Theoretically, all could coexist, and if they were all of equal importance the removal of any one would not affect blood pressure levels. If one is dominant, its removal should be followed by a lowering of the blood pressure level to that at which the others are operating and in their absence to normal.

The mortality in hypertensive patients is due to complications particularly in the cardiac, cerebral and renal areas. That mortality is high is well known and it is believed that there are more deaths per year from hypertensive cardiovascular disease than from any other disorder of mankind. In a recent series of 156 unselected, untreated hypertensive patients who were carefully studied and found to have continued hypertension with evidence of cardiovascular disease varying from slight to marked, we found the mortality to be 26.9 per cent in a follow-up period averaging 5.6 months. These patients had been referred for consideration of surgical treatment and doubtless represented the more severe and advanced forms of the disorder. It is of interest that Bechgaard[4] recently reported a mortality rate of 28.2 per cent in a series of 1,038 hypertensive patients followed seven to eleven years. This indicates how widely mortality statistics may vary in different series of patients.

As previously indicated, mortality in the earlier stages of hypertension is low because cardiovascular damage of consequence rarely occurs until the stage of continued hypertension is reached. When cardiovascular damage appears in the stage of intermittent hypertension, surgical intervention should be considered. The principal indication for surgery is the presence of continued hypertension with evidence of cardiovascular damage. The purpose is to lower blood pressure levels and to decrease the magnitude of reflex variations in blood pressure by modifying the neurogenic component of peripheral resistance. The rationale is the belief that elevated blood pressure and the associated vasomotor fluctuations accelerate the progress of cardiovascular disease and its fatal complications. The principal contraindications to surgery are the circumstances which we have found from experience to indicate with reasonable certainty that the result of operation will not be worth while. In order to exclude these patients it is necessary to have certain information. This is obtained by subjecting each patient to a standard method of study.

METHOD OF STUDY

An outline of the method of study used is given because the data serve as a basis for dividing subjects into a number of groups. If this information is available, it is then possible to tell whether a given patient falls into the so-called selected or into the excluded group. In general, I would advise those who are beginning to interest themselves in this problem to advise against operation in patients who fall into the excluded group. It is true that some individuals in the selected group will do poorly and some in the excluded group will do well. It is expected that further experience and more detailed studies will make it possible to identify these exceptions with increasing accuracy. Further considerations of this matter are contemplated in the future.

In addition to a detailed history and physical examination, the eyegrounds with fully dilated pupils should be examined by an ophthalmologist. Occasional patients

with continued hypertension have normal eyegrounds. A simple classification has been used which divides the abnormal patients into four grades:

(1) Subjects with spasm only, generalized narrowing or irregular constrictions, or both, of any degree, without evidence of sclerosis and without hemorrhage, exudate or papilledema; (2) sclerotic changes, particularly arteriovenous compression, generally associated with tortuosity and increased light reflex. Spasm may also be present but hemorrhage, exudate and papilledema should not be in evidence; (3) patients with hemorrhage and/or exudate but without papilledema regardless of the changes in the vessels; (4) papilledema with measurable elevation of the disk, generally associated with hemorrhage, exudate and changes of consequence in the retinal arteries.

Cardiac status is determined by a cardiologist, supplemented by an electrocardiogram and a seven foot heart plate with particular reference to the size and shape of the heart and the state of the aorta. The renal area is evaluated by urinalyses, a twelve-hour concentration test and an intravenous phenolsulphonphthalein test (the dye being injected after a period of forced fluid intake and specimens collected at intervals of fifteen and thirty minutes and one and two hours). This ordinary test of renal function has been found useful in estimating the extent of renal damage in hypertensive patients and is the one we have come to rely upon most. A non-protein nitrogen determination is made and intravenous pyelograms are obtained routinely. Blood studies include counts, smears, hemoglobin determinations, blood grouping, Rh factor, Hinton test and determinations of blood sugar, serum protein, cholesterol and chlorides. If a cerebral vascular accident has occurred, a neurologic consultation is requested and such additional studies as skull plates, electroencephalograms and lumbar puncture are carried out as seems indicated.

A postural and cold blood pressure test is performed as follows: the patient is required to have at least forty-eight hours of bed rest except for lavatory privileges. Following this preliminary period, tests are carried out by technicians rather than by physicians since the former are generally able to obtain lower readings, presumably because physicians often act as a pressor stimulus to the patient. Preliminary readings of blood pressure are taken on each arm. If no great discrepancy exists, the right arm is used. If there is a marked difference on the two sides, this is checked a number of times and the arm with the higher reading is selected. The test is explained to the patient and, after an additional rest period of fifteen to twenty minutes in the horizontal position, observations are begun. It is essential that the environment be quiet, comfortable and pleasant. Ward patients are transported to a special room for performance of the test, during which there should be no interruptions. Readings of pulse and blood pressure are taken every minute for five minutes with the patient lying, sitting and standing. The horizontal position is again assumed and five further readings at minute intervals are taken, following which the opposite hand is immersed in ice water (4° to 5°C.) up to the wrist for exactly one minute and readings are taken after thirty seconds and at the end of the sixty seconds of stimulation by cold. Readings are then continued at one-minute intervals for an additional five minutes. The patient then assumes the upright position and after five preliminary readings at one-minute intervals the cold stimulus is repeated exactly as in the horizontal position.

The average of the five readings in the horizontal position in the first portion of the test is called the resting blood pressure level and is used to divide patients into three types, the purpose of which is to arrange them into similar categories according to the width of the pulse pressure in the resting horizontal position. In general, in both males and females the wider the pulse pressure the poorer the statistical

chances for lowering the blood pressure. In type I, the pulse pressure is less than one-half the diastolic pressure. In type II, the pulse pressure is equal to or up to 19 mm. more than one-half the diastolic pressure. In type III, the pulse pressure is 20 mm. or more greater than one-half the diastolic pressure.

A sedative test is performed in all patients. Following a light supper, three grains of sodium amytal are given by mouth at 6:00, 7:00 and at 8:00 P.M. Hourly readings of pulse and blood pressure are recorded from 7:00 P.M. to 7:00 A.M. The lowest reading of systolic and diastolic blood pressure is taken as the response. This is evaluated by comparison with the horizontal or resting blood pressure level as determined by the postural and cold test and the diastolic response is regarded as the most significant figure. For patients with resting diastolic levels in the postural and cold test below 120 mm., the diastolic response to sedation should be to 90 or less; for those in the range of 120 to 129 mm., it should be to 100 or less; and for those with resting levels of 130 mm. or more it should be to 110 mm. or less in order to be regarded as satisfactory. Better responses than this not infrequently occur and are regarded as good or excellent. A lesser response also is not uncommon and is regarded as poor.

SELECTION OF CASES FOR SURGERY

With the above information it is possible to determine whether a patient falls into the selected or the excluded group. An individual may be regarded as being in the latter category if any of the circumstances under which the results of operation are most likely to be unsatisfactory apply. These determining circumstances are divided into two groups, A, general, and B, more specific. The latter were compiled by dividing the patients into twelve groups according to age, i.e., below forty and forty and over, and two sexes and three types. The resting diastolic level, the state of the brain, eyegrounds, heart and kidneys, as well as the response to sedation, were also taken into consideration.

The circumstances under which operation has been found most likely to be unsuccessful are as follows:

A. (1) When nitrogen retention is present; (2) when actual or impending congestive heart failure is associated with poor kidney function (intravenous phenolsulphonphthalein output less than 15 per cent in fifteen minutes and 50 per cent in two hours); (3) when renal function is poor but the cardiac status satisfactory if the patient has had a cerebral vascular accident or has grade (3) or (4) eyeground changes. Possible exceptions are subjects with known pyelonephritis or an unusually marked response to sedation or both; (4) when the cardiac changes are marked (actual or impending congestive heart failure) and the renal function is satisfactory (intravenous phenolsulphonphthalein output 15 per cent in fifteen minutes and 50 per cent or more in two hours) in the presence of a cerebral vascular accident or grade (3) or (4) eyeground changes. Possible exceptions are patients with known pyelonephritis or a remarkable response to sedation or both. Operation may be considered if the renal function is normal and the response to sedation satisfactory. The heart, however, must be well compensated and must have responded well to medical measures.

B. If the preceding circumstances do not apply to a particular patient the following criteria should also be considered before advising surgical treatment:

1. Type I Males. If the resting diastolic level is less than 120, operation may be performed if the general suggestions do not apply. For diastolic levels 120 to 130, age thirty-eight or more, it has been noted that these patients who have had a cerebral vascular accident or have grade (3) or (4) eyeground changes have done poorly unless the response to sedation is satisfactory and the electrocardiogram or renal function is normal (intravenous phenolsulphonphthalein output 25 per cent in fifteen minutes and 50 per cent or more in two hours).

If either the electrocardiogram or kidney function is abnormal, the changes should be slight at most. When the resting diastolic level is 140 mm. or more, the outlook is poor in general. Operation in these individuals seems inadvisable if there has been a cerebral vascular accident, encephalopathy, congestive heart failure, or more than slight impairment of renal function (intravenous phenolsulphonphthalein output 20 per cent in fifteen minutes and 50 per cent or more in two hours). If the patient has grade (2), (3) or (4) eyeground changes, the electrocardiogram should be normal. If the eyegrounds are normal or grade (1), operation may be performed if the cardiac and renal changes are slight at most.

2. Type I Females. If the resting diastolic level is below 120, operation may be performed if the general suggestions do not apply. If the resting diastolic level is 120 or more and the patient has had a cerebral accident, encephalopathy or has grade (3) or (4) eyeground changes, operation may be performed if the cardiac and renal functions and the response to sedation are satisfactory. If the response to sedation is poor and the patient is under thirty-eight years of age, the result may be worth while if the electrocardiogram is normal or chronic pyelonephritis is known to exist.

3. Type II Males. Patients under forty years of age to whom the general suggestions do not apply, have done poorly when the resting diastolic level is below 110 mm. and grade (3) eyeground changes are present. Male patients in this same age group with resting diastolic levels of 130 mm or more have done poorly unless the changes in all areas are minimal at most. Male patients type II, age forty and over, have done poorly at all diastolic levels if the response to sedation is poor. Also, if the response to sedation is satisfactory and the resting diastolic level is 120 mm. or more, the results have been poor when renal function has been poor (intravenous phenolsulphonphthalein output of less than 15 per cent in fifteen minutes and 50 per cent in two hours). If the response to sedation is satisfactory and the resting diastolic level is 120 mm. or more and the eyegrounds are grade (3), the results have been poor unless renal function is good (intravenous phenolsulphonphthalein output 20 per cent in fifteen minutes and 50 per cent or more in two hours).

4. Type II Females. Below the age of forty these patients have done unusually well when the general suggestions do not apply. Patients age forty and over to whom the general suggestions do not apply have not done well if there has been a cerebral accident and the eyegrounds are grade (3) or (4). Also type II females, age forty-five and over, have in the great majority of instances done poorly if the response to sedation is unsatisfactory.

5. Type III Males. Below the age of forty operation may be performed if the general rules do not apply except in patients with eyeground changes greater than normal or grade (1), unless the renal function is normal (intravenous phenolsulphonphthalein output 25 per cent in fifteen minutes and 50 per cent or more in two hours). Patients age forty and over have done poorly if the response to sedation is poor. Patients age forty-five and over with grade (3) eyegrounds and abnormal electrocardiograms have done poorly when the renal changes are more than slight (intravenous phenolsulphonphthalein output less than 20 per cent in fifteen minutes and 50 per cent in two hours).

6. Type III Females. Below the age of forty these patients have done unusually well if the general suggestions do not apply. If the age is forty or over, patients who have had a cerebral accident have done poorly unless the eyegrounds are normal or grade (1) and the diastolic response to sedation is to below 80. Patients age forty and over with resting diastolic levels of 130 mm. or more have done poorly.

EARLY RESULTS

In a group of 439 patients with continued hypertension and slight to marked cardio-

vascular changes, these rules were found to apply to 120 of the patients and were found not to apply to 319 subjects. These patients were followed by the author and associates for a period of from one to five or more years. The results in each group are shown in Tables I, II and III, respectively. The results have been judged both by the effect upon blood pressure and the effect on cardiovascular disease.

TABLE I*

A SERIES OF 439 UNSELECTED PATIENTS WHO HAVE BEEN OPERATED UPON AND FOLLOWED FOR ONE TO FIVE OR MORE YEARS

Blood Pressure

	Improved			Unchanged		Higher	Deaths
	1	2	3	4	5	6	7
Per cent	22.8	14.5	28.9	6.6	5.8	6.8	14.6
Total (per cent)	66.2			12.4			

Cardiovascular Disease

	Improved	Unchanged	Equivocal	Worse
	A	B	C	D
Per cent	61.7	10.0	9.2	19.1

*These patients have been divided into two groups in Tables II and III, the so-called excluded and selected cases.

The effect upon blood pressure is tabulated as improved, unchanged, higher and deaths. The effect upon cardiovascular disease has been tabulated as improved, unchanged, equivocal or worse. The effect upon blood pressure was divided into seven categories which are as follows: (1) diastolic pressure lowered 20 mm. or more, and to below 90; (2) diastolic pressure lowered 20 mm. or more, but not to below 90; (3) diastolic pressure lowered less than 20 mm. to no change at all, pulse pressure definitely narrowed and ceiling levels lowered; (4) diastolic level and pulse pressure essentially unchanged but ceiling levels lowered; (5) no change in blood pressure; (6) blood pressure higher and (7) deaths.

Blood pressure changes graded as 1, 2 or 3 comprise the improved group; those graded 4 and 5, unchanged; those graded 6, higher; those graded 7 include the deaths.

The effect upon cardiovascular disease has been graded as follows: A, this group contains subjects with favorable changes in one or all areas with no evidence of progress in any area. B, in this group are subjects in which there is no evidence of reversal or improvement in any area but also no evi-

TABLE II

SERIES OF 120 PATIENTS HAVING CONTINUED HYPERTENSION AND CARDIOVASCULAR CHANGES WHO HAVE BEEN OPERATED ON AND FOLLOWED FROM ONE TO FIVE OR MORE YEARS AND WHO WOULD BE EXCLUDED BY THE RULES

Blood Pressure

	Improved			Unchanged		Higher	Deaths
	1	2	3	4	5	6	7
Per cent	2.5	5.8	7.5	7.5	8.3	16.7	51.7
Total (per cent)	15.8			15.8			

Cardiovascular Disease

	Improved	Unchanged	Equivocal	Worse
	A	B	C	D
Per cent	23.3	6.7	10.8	59.2

TABLE III

SERIES OF 319 PATIENTS HAVING CONTINUED HYPERTENSION AND CARDIOVASCULAR CHANGES WHO HAVE BEEN OPERATED ON AND FOLLOWED ONE TO FIVE OR MORE YEARS TO WHOM THE RULES DO NOT APPLY AND WHO WOULD NOT BE EXCLUDED BY THEM

Blood Pressure

	Improved			Unchanged		Higher	Deaths
	1	2	3	4	5	6	7
Per cent	30.1	17.6	37.1	6.2	5.4	2.4	1.2
Total (per cent)	84.8			11.6			

Cardiovascular Disease

	Improved	Unchanged	Equivocal	Worse
	A	B	C	D
Per cent	76.2	11.3	8.5	4.0

dence of progression. C, in this group fall subjects in which there is evidence of improvement in one or more areas but also evidence of progress of cardiovascular disease in another or other areas. D, these subjects show no evidence of improvement or no change in one or more areas associated with evidence of progression in one or more areas. Deaths are also placed in this group.

Subjects graded as A are tabulated as improved; B, unchanged; C, equivocal; D, worse.

TABLE IV
SURGICAL TREATMENT OF HYPERTENSION
Early Results of Sympathectomy and Splanchnioectomy by Various Technics in Patients Followed from Months to Five Years or More

Author	No. Cases	Subjective and Objective Improvement	Subjective Improvement, No change, or Worse	Deaths
		(per cent)	(per cent)	(per cent)
Allen and Adson[5] (1940)	224	31.0	53.8	15.2
Peet, Woods, Braden[6] (1940)	350	42.6	26.8	30.6
Hammarström[7] (1947)	82	54.9	18.2	26.9
Smithwick[3] (1947)	439	61.7	23.7	14.6
Poppen and Lemmon[8] (1947)	100	71.0	22.0	7.0
Grimson[9] (1946)	41	76.0	6.3	17.7
Late Results of Supradiaphragmatic Splanchnicectomy in Patients Followed for Five to Twelve Years				
Peet[10] (1946)	437	46.7	8.1	42.5

In Table IV, the early results of sympathectomy and splanchnicectomy by various technics[3,5–10] are summarized. These appear to me to be representative reports from the literature. I have taken the liberty of arranging the results under certain headings and estimating the percentages from the data appearing in the articles. This was necessary because no standard method of reporting results has been used. I believe the general impression of the results as judged by the various authors themselves has not been materially altered. Only one report of late results in a large series of cases has so far appeared in the literature. This report by Peet[10] is also summarized in Table IV.

We believe that these results are poor and that the statistical chances for improvement are not great enough to justify surgery in patients falling into this category.

We believe the results in this series are much better and for the most part seem worth while for the period of observation. These results are approximately what one may anticipate if patients are operated upon who are not excluded by the rules. The majority of these patients have been followed for less than three years. A longer follow-up will no doubt reveal that operation was not worth while in some of them. A follow-up study of patients operated upon five or more years ago is now in progress. This should give a more accurate idea of the long range outlook for surgically treated patients. It is hoped that these data will make it possible to establish criteria which will insure a satisfactory late result in a high percentage of patients.

PHYSIOLOGIC EFFECT OF EXTENSIVE SYMPATHECTOMY UPON BLOOD PRESSURE LEVELS AND VASOMOTOR RESPONSES

In the patients referred to in Tables I, II and III, the operation performed was lumbodorsal (thoracolumbar) splanchnicectomy. The minimal procedure should be the removal of the sympathetic trunks bilaterally from D_8 to L_1 inclusive. The great splanchnic nerves are removed from the celiac ganglia to the mid-thoracic level. In some subjects resection of the trunks was more extensive. We are not certain that more extensive resections are more effective. The operation is performed in two stages spaced ten days apart. This operation fulfills certain criteria which we believe to be important: (1) minimal operative mortality and morbidity; (2) maximal possibilities for blood pressure reduction; (3) maximal reduction of reflex variations in blood pressure; (4) maximal protection against regeneration; (5) absence of serious untoward effects; (6) provision for exploration of adrenal glands and adequate exposure for the removal of tumors; and (7) provision

for inspection and biopsy of kidneys and exposure for nephrectomy if indicated.

During the last year or two, we have performed subtotal to total thoracic sympathectomy in two groups of patients and believe that these procedures may prove to be preferable to lumbodorsal splanchnicectomy under certain circumstances. First are patients with hypertensive cardiovascular disease with angina pectoris. In these the sympathetic trunks were removed bilaterally from the inferior cervical to the twelfth thoracic ganglia inclusive, together with the splanchnic nerves arising from these segments. Second is a group of patients with hypertensive cardiovascular disease and unusual tachycardia. In these the trunks were removed from the second to the twelfth thoracic ganglia. The operations were performed in two stages about two weeks apart. The results in these patients will be reported at a later date. They are mentioned at this time because the physiologic effect seems comparable, quantitatively speaking, to that following lumbodorsal splanchnicectomy, particularly as regards modification of vasomotor responses.

Two physiologic effects of extensive sympathectomy upon blood pressure are (1) changes in levels and (2) modification of vasomotor responses. These consist of a lowering of diastolic pressure, a narrowing of the pulse pressure and reduction of ceiling levels following stimulation. Reference to Table 1 indicates the percentage of unselected subjects having these various modifications of blood pressure levels. It will be noted that a grade (1) effect was obtained in 22.8 per cent of the patients. The blood pressure levels of 100 hypertensive patients who obtained grade (1) results compared favorably with those of a control series of 100 normotensive patients studied in the same fashion. The hypertension was largely reversible in these patients, suggesting that increased peripheral resistance to blood flow in certain hypertensive patients can be markedly decreased by splanchnicectomy. (Fig. 1.) Two subjects with grade (1) results are illustrated in Figures 2 and 3; these are typical examples of patients ideally suited for surgical treatment. A poor candidate for surgery is illustrated in Figure 4.

Modification of vasomotor responses has been regularly observed by Wilkins and Culbertson[11,12] in response to various stimuli following lumbodorsal or total thoracic sympathectomy. The same is true after total sympathectomy. These responses are not abolished after lesser maneuvers such as subdiaphragmatic or supradiaphragmatic splanchnicectomy. Following lumbodorsal or total thoracic sympathectomy, vasomotor responses following the Valsalva maneuver are almost always completely abolished. (Fig. 5.) It seems probable that reversal of cardiovascular damage existing prior to operation is due in part to decreased stress and strain upon the vascular bed resulting from modification of reflex vasomotor variations in blood pressure. This physiologic effect together with lowering of blood pressure levels are probably the two most important changes after extensive sympathectomy. Other possible effects, such as elimination of reflex secretion of adrenalin, decreased production of sympathin and the stabilization of blood flow through the denervated area, are perhaps of lesser importance. Favorable changes in eyegrounds, electrocardiograms, heart size and renal function as judged by ordinary tests have been described in other communications.[13–17]

UNTOWARD EFFECTS OF EXTENSIVE SYMPATHECTOMY

Following extensive sympathectomy, certain undesirable effects are noted. The denervated areas do not perspire, consequently sweating is increased in the undenervated areas. Also, vasomotor responses are abolished in denervated areas and increased in undenervated regions. Consequently, excessive perspiration in the upper portion of the body and cold hands are commonly noted after lumbodorsal or thoracolumbar splanchnicectomy. The same changes are noted in the lower extremities after total thoracic sympathectomy. These

effects are unpleasant but not serious and decrease with the passage of time. Postural hypotension with tachycardia is present after lumbodorsal splanchnicectomy and without tachycardia after total or subtotal thoracic sympathectomy. Leg bandages or elastic stockings and a lower abdominal girdle are used to counteract these effects in the early postoperative period. These changes gradually disappear after four to six months in the great majority of patients. The basal pulse rate is slower after both procedures, markedly so after total and subtotal thoracic sympathectomy. In an occasional patient, tachycardia in response to exercise persists to a troublesome degree after lumbodorsal splanchnicectomy. In two patients it was necessary to denervate the heart at a later date to abolish this difficulty. In retrospect, both patients had unusual tachycardia prior to operation and in such patients we now include cardiac denervation as part of the original maneuver.

Abolition of ejaculation regularly follows extensive removal of the lumbar outflow. If both first lumbar ganglia only are removed, ejaculation is preserved in the great majority of individuals. If preservation of this function is imperative, the lumbar outflow on one side should be left intact. Orgasm is not affected. Impotence is rare after operations of any magnitude. It is difficult to explain its occurrence on a physiologic basis since erection is mediated by the parasympathetic division of the autonomic nervous system.

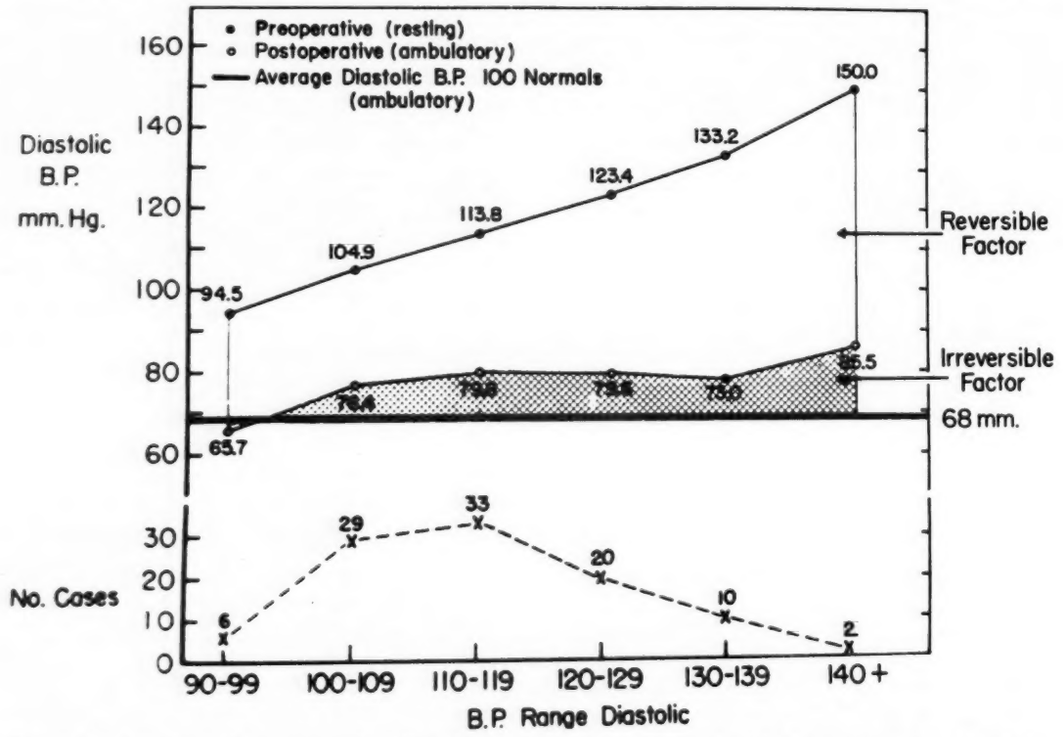

FIG. 1. In this chart the preoperative diastolic pressures are compared with the postoperative levels in one hundred patients who obtained a grade 1 result. Preoperative levels were determined after forty-eight hours of bed rest; postoperative levels were ambulatory and were obtained after fifteen or twenty minutes' rest in a horizontal position. The patients are divided into groups according to the height of the preoperative diastolic levels. The levels for all patients with pressures falling within each 10 mm. range were averaged. The average of the postoperative values for these same patients are charted immediately beneath. A base line of 68 mm. of mercury is used for comparison since this was found to be the average diastolic level of one hundred normotensive individuals studied in an ambulatory fashion by technicians after fifteen or twenty minutes' rest. The chart indicates that in these patients the hypertension was largely reversible at all diastolic levels. This suggests that in certain patients with continued hypertension the nervous system may be largely responsible for the increased tone of arteriolar smooth muscle. Examples of grade 1 results are illustrated in Figures 2 and 3.

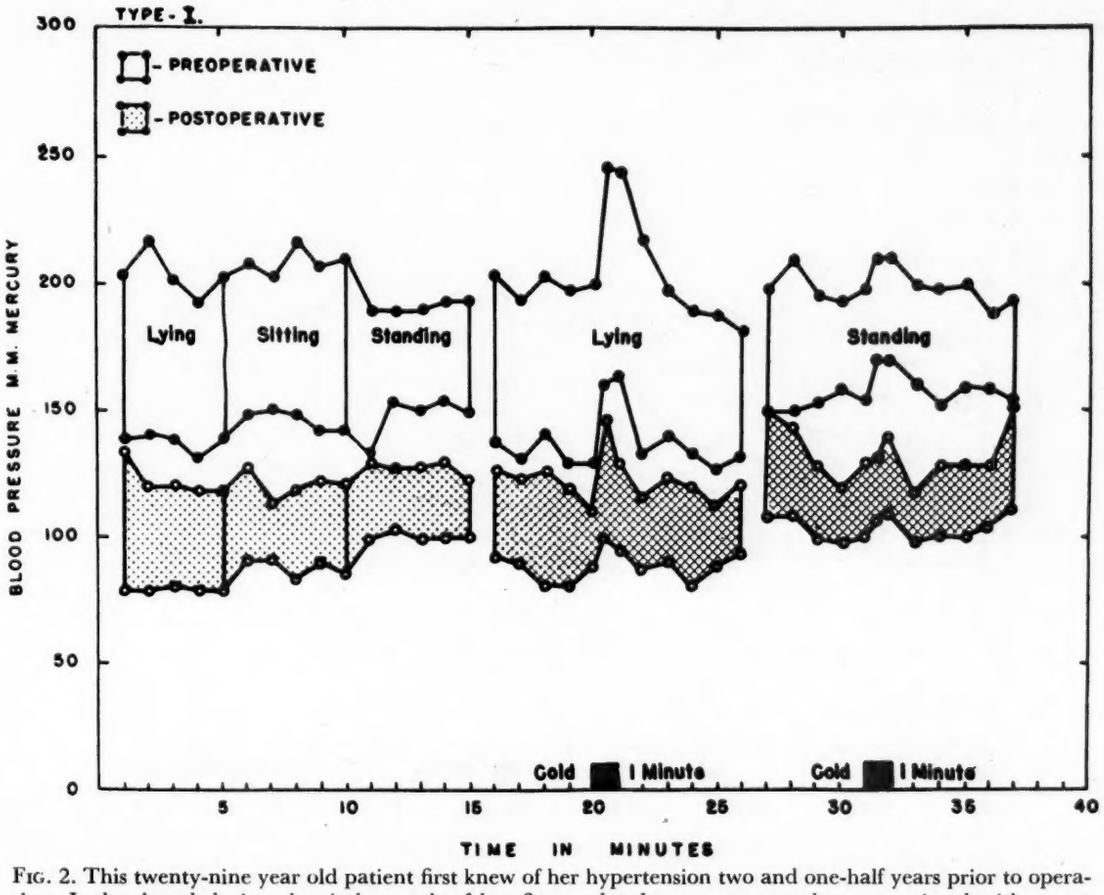

FIG. 2. This twenty-nine year old patient first knew of her hypertension two and one-half years prior to operation. It developed during the sixth month of her first and only pregnancy and was associated with severe toxemia necessitating termination of the pregnancy. The fetus was not viable. Since that time, hypertension persisted and remained severe. This was associated with frequent severe headaches. Various therapeutic measures were ineffective, including x-ray treatment of the pituitary. The retinal arteries were diffusely narrowed and irregular and there was some increased tortuosity. There were scattered exudates; the electrocardiogram was normal and the heart was slightly enlarged and the aorta tortuous. Renal function was satisfactory by ordinary tests, with persistent albuminuria. On sedation the blood pressure fell to 126/84. The blood pressure levels before and thirteen months after operation were as follows:

	Lying	Standing	Ceiling Cold		Cold Response	
			Lying	Standing	Lying	Standing
Preoperative (resting)	196/132	194/147	230/172	230/170	30/34	54/30
Postoperative (ambulatory)	122/78	128/100	146/100	138/108	34/12	8/8

Examination of the cardiovascular system revealed normal eyegrounds, normal electrocardiogram, normal heart size and normal renal function. The patient is extremely anxious to have a child and was told that in view of previous experiences with pregnancy, following a good response to operation that it would be safe for her to have a further trial of pregnancy.

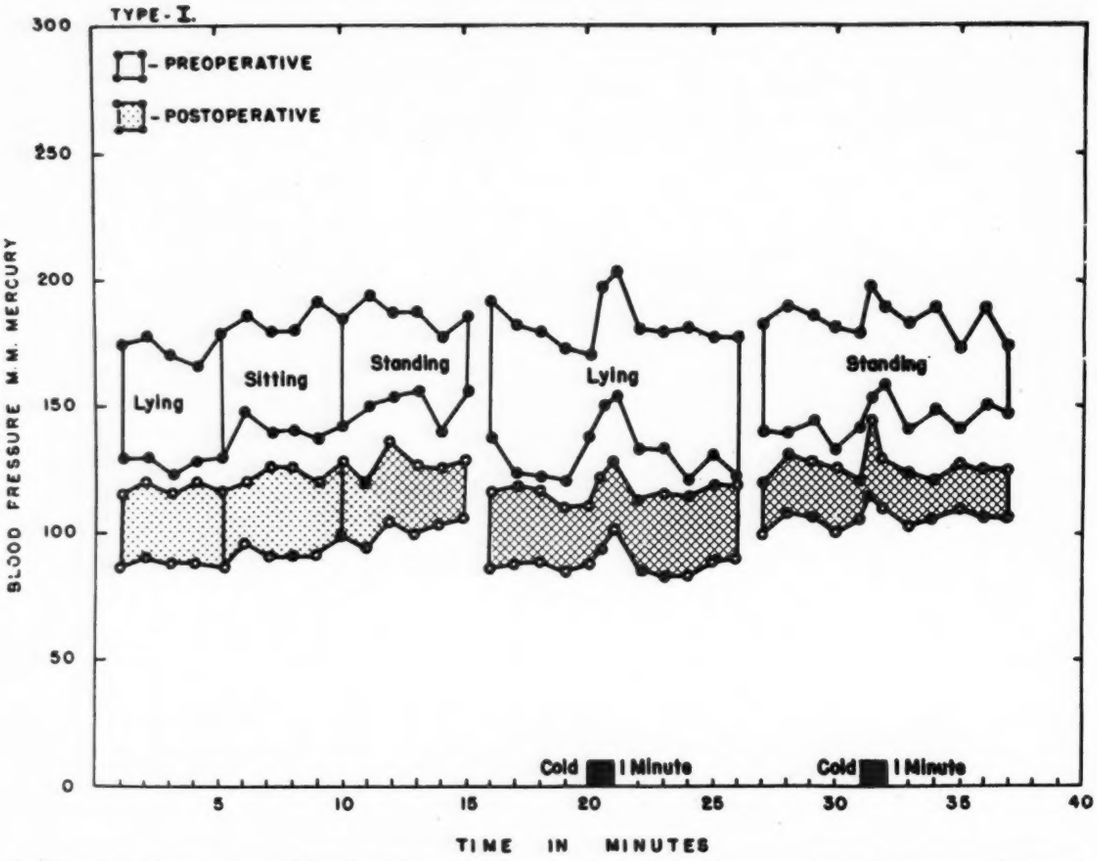

FIG. 3. This thirty-six year old police officer was found to have severe hypertension with eyeground changes which consisted of marked beading and irregular constrictions of the retinal arteries with scattered hemorrhages and one diopter of papilledema. So far as he knew the hypertension was of less than one year's duration. Occipital headaches in the morning and ease of fatigue were the principal symptoms. Aside from the eyegrounds and early electrocardiographic changes, the cerebral, cardiac and renal areas were apparently normal. His blood pressure fell to 130/90 on sedation. His blood pressure levels before and at intervals after operation are tabulated. Those before and five years after operation are illustrated as follows:

	Lying	Standing	Ceiling Cold		Cold Response	
			Lying	Standing	Lying	Standing
Preoperative (resting)	175/120	189/152	204/154	198/160	36/16	18/18
Postoperative (ambulatory) (12 mo.)	127/90	132/105	124/104	150/118	−10/+10	12/10
(41 mo.)	113/80	128/94	110/90	124/94	0/12	4/6
(60 mo.)	118/86	128/102	130/102	144/116	18/14	20/10

It is of interest that the renal biopsy material revealed very advanced chronic vascular nephritis, grade 4. This patient, as well as the patient illustrated by Figure 2, are the best candidates for surgery. They have the following features in common which are indicative of a worth while result: narrow pulse pressure (types I and II), younger age group, variable hypertension with hyper-reactivity, not too severe cardiovascular damage and a good response to sedation.

PREGNANCY FOLLOWING LUMBODORSAL SPLANCHNICECTOMY

An increasing number of patients are being permitted to attempt pregnancy following a favorable response to extensive sympathectomy. The course of pregnancy in fourteen patients was recently discussed by Newell and Smithwick.[18] These patients had continued hypertension with varying degrees of cardiovascular damage prior to splanchnicectomy. Approximately half of the patients had chronic pyelonephritis. Three patients had malignant hypertension. The time elapsing between the diagnosis of hypertension and operation averaged seventy-five months. The time between operation and pregnancy averaged thirty months with the exception of one woman

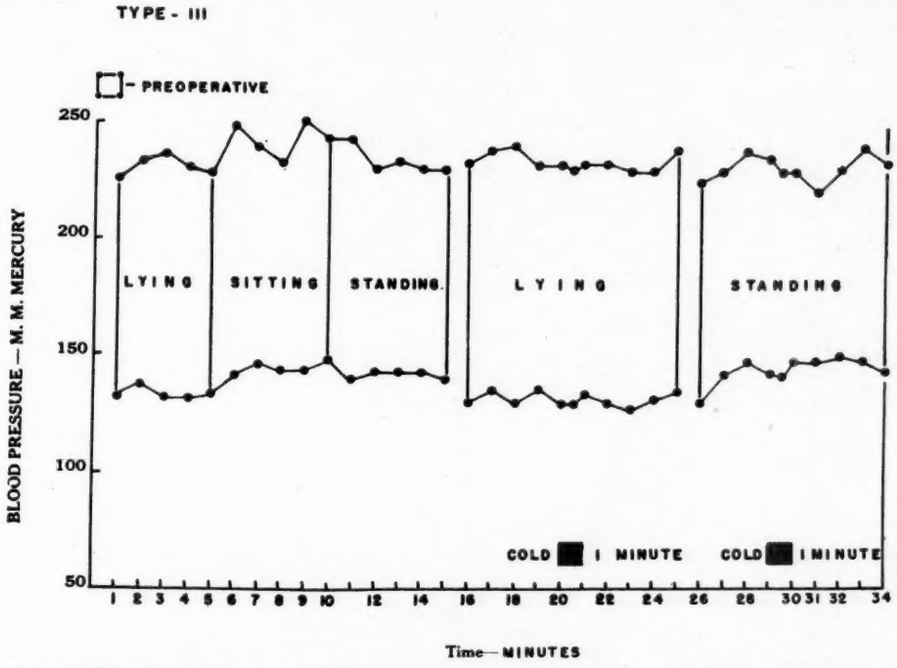

FIG. 4. This thirty-nine year old female patient is illustrative of some of the circumstances under which operation is most likely to fail to modify the hypertensive state. About six months prior to admission she suffered a cerebral vascular accident from which she had recovered satisfactorily without much residual. Her eyegrounds showed marked changes in the arteries with hemorrhages, exudate and papilledema. Her heart was enlarged and she had early congestive failure. The electrocardiogram was abnormal. Her renal function was markedly impaired as judged by ordinary tests. The non-protein nitrogen was within normal limits. There was no response to sedation. The blood pressure levels as determined by the postural and cold test after a period of bed rest are illustrated and were high and fixed. The pulse pressure was wide (type III).

	Lying	Standing	Ceiling Cold		Cold Response	
			Lying	Standing	Lying	Standing
Preoperative (resting).....	230/134	236/142	234/134	230/148	2/4	−6/+4

This patient was operated upon and died within a year of a recurrent cerebral accident. There was no change in her blood pressure levels after operation. From experiences of this sort we have learned that patients who fall into certain categories are poor candidates for surgery and should be excluded. Many patients of this sort are in Table II and are commented upon in greater detail in the text.

on whom splanchnicectomy was performed during the first trimester. Admission blood pressure levels prior to splanchnicectomy averaged 196/130, prior to pregnancy 135/87, two weeks post partum 134/89, and six or more weeks post partum 133/87. All but one patient obtained a living child and did not appear to have suffered cardiovascular damage. One still birth resulted from premature separation of the placenta. This patient subsequently obtained a living child at a second pregnancy. In nine women the pregnancy was entirely uneventful without elevation of blood pressure or signs of toxemia. In five, signs of toxemia with elevation of blood pressure varying from slight to marked necessitated termination of the pregnancy. All obtained living children as this complication occurred late in pregnancy. The series has increased considerably. Two additional patients having severe continued hypertension were operated upon in the first trimester and delivered uneventfully at term. Several other patients, one with large bilateral polycystic kidneys, have become pregnant at various time intervals after operation and all have had an uneventful course and obtained living babies. It is our impression that following a satisfactory response to opera-

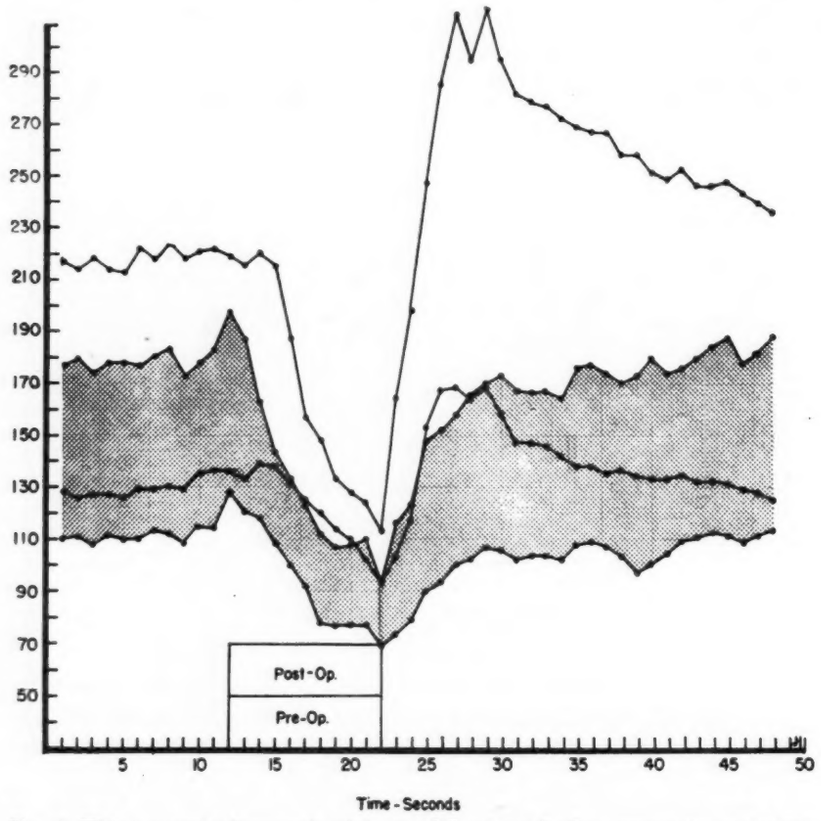

FIG. 5. This is a typical example of the modification of reflex vasomotor variations in blood pressure following thorough denervation of the splanchnic bed. Intra-arterial blood pressure levels are optically recorded with a Hamilton manometer before, during and after the Valsalva maneuver. The latter consists of exhaling against a positive pressure of about 40 mm. of mercury for ten seconds which causes a sharp fall in blood pressure. The sharp overshoot which follows within a few seconds before operation is compared with the abolition of this phenomenon after operation (shaded graph). This indicates that denervation of a large vascular area minimizes reflex vasomotor variations in blood pressure. This should decrease stress and strain upon the vascular bed. This physiologic effect of sympathectomy occurs in all thoroughly denervated patients and is unrelated to changes in blood pressure levels.

tion, pregnancy, if carefully supervised, appears to be safe and permissible. These experiences lead us to believe that following this operation certain hypertensive women may be able to tolerate pregnancy which would otherwise be impossible or extremely hazardous. This is particularly true in the younger age group with severe essential and even malignant hypertension, with or without chronic pyelonephritis.

UNILATERAL NEPHRECTOMY

The removal of one kidney in hypertensive patients should be undertaken with caution. The number of hypertensive patients who might benefit from such a procedure is small and is thought to be less than 1 per cent of all. Opinions vary as to the rationale for this procedure. It is based upon the experimental work of Goldblatt who demonstrated clearly that transient hypertension follows partial clamping of one renal artery in dogs. More persistent hypertension can be produced in other animals in this way, particularly in rats. If the clamp or the kidney is removed, the hypertension disappears.

A critical analysis of the results of unilateral nephrectomy by Goldring and Chasis[19] led them to believe that 10 per cent of patients so treated were improved. Two recent reports by Ratliff et al.[20] and Barker and Braasch[21] are more optimistic. They indicate that moderate improvement lasting for years may be expected in about one-third of the patients and slight improvement in an additional 15 per cent. It should be emphasized that only seriously affected or non-functioning kidneys should be removed. The function of the remaining kidney should be little if at all impaired. It seems inadvisable to remove the poorer of two involved kidneys. In general, the indications for nephrectomy in hypertensive patients should be essentially the same as in non-hypertensive patients. Unilateral nephrectomy may be combined with lumbodorsal splanchnicectomy providing infection does not contraindicate such a procedure.

ADRENAL TUMORS AND PARAGANGLIOMAS

Adrenal tumors have been present in about 4 per cent of the hypertensive patients operated upon by the author. About 90 per cent of these are cortical adenomas and their relation to the hypertensive state is not as yet clear. Only one of these was clearly an important factor. Ten per cent of the tumors have been pheochromocytomas and with one exception they have been physiologically active. Ninety per cent of these patients have a definite history of paroxysmal attacks of hypertension associated most commonly with headache, palpitation, vomiting and sweating. Ten per cent have no such symptoms. To confuse the issue further, adrenal tumors have been more commonly absent than present in paroxysmal forms of hypertension in my experience. While there are other suggestive findings such as hypermetabolism, hyperglycemia, an active pressor response to histamine or acetylcholine, a normal or decreased response to stimulation by cold or postural hypotension associated with tachycardia, none of these signs is absolutely diagnostic. In some instances a tumor can be felt but this is rare in my experience. An attack may be precipitated by massage, straining or emotion. The diagnosis may be suggested by intravenous pyelography or perirenal air injection. The latter is not without danger. The only certain and safe way to make the diagnosis is to explore the adrenal glands. As previously stated, this should be a part of any widely utilized operation in hypertensive patients. It is important that the diagnosis be made since the effect of removing physiologically active tumors is almost always dramatic. It is unfortunate that the diagnosis has so far been made most frequently at autopsy.

SUMMARY

There are three surgical measures which may be helpful in the management of hypertensive patients.

Unilateral nephrectomy appears to have modified the course of the disorder in some

patients. It appears to be difficult or impossible to predict the outcome. It seems permissible to remove a seriously damaged or non-functioning kidney when the other is little if at all affected. It seems unwise to remove the poorer of two involved kidneys. In general, the indications for nephrectomy should be the same in hypertensive as in non-hypertensive patients.

The removal of adrenal tumors which are physiologically active is helpful. In those patients having paroxysmal hypertension the diagnosis can often be made with considerable certainty. On the other hand, paroxysmal forms of hypertension may not be due to tumors but appear to be the result of an intermittent increase in diencephalic activity. In these patients denervation of the splanchnic bed has been effective. Continued non-paroxysmal hypertension may be caused by an adrenal tumor. The diagnosis may be difficult to make and most of these tumors have been found unexpectedly during the course of operations upon the sympathetic nervous system. In general, active adrenal tumors are rare causes of hypertension. They almost always prove to be pheochromocytomas.

Surgical intervention upon the sympathetic nervous system appears to offer many patients a reasonable chance for improvement at a minimal risk. It appears to slow the progress of the disorder. It probably is rarely if ever curative. A lessening of the severity of cardiovascular damage, as judged by favorable changes in the retinal, cardiac or renal areas, was noted in about 60 per cent of unselected patients followed from one to five or more years. Blood pressure levels were also modified slightly to markedly in about 60 per cent of these subjects. It is believed that at least part of the effect of the operation is due to a modification of reflex vasomotor fluctuations in blood pressure. This effect is independent of changes in blood pressure levels and occurs in virtually all thoroughly denervated patients. It is possible that elimination of reflex secretion of adrenalin and a stabilization of blood flow through the denervated area may be of some importance.

Extensive sympathectomy has been utilized largely in patients who have reached the stage of continued hypertension with evidence of cardiovascular damage varying from slight to marked. Experience to date indicates that at least 30 per cent of these patients are clearly unsuited for this form of treatment and rules have been formulated in an attempt to exclude them as far as possible. If such patients are excluded, the early results in the remaining subjects are considerably better. A follow-up period of five years or more is needed to establish the circumstances under which splanchnicectomy is most likely to be worth while. It is gradually becoming apparent that patients with the best chance for good results are those in the younger age groups with narrower pulse pressures, (types 1 and 2) with variable blood pressures, the cardiovascular systems not too extensively damaged and with satisfactory responses to sedation. Two typical examples of patients ideally suited for surgical treatment are illustrated in Figures 2 and 3. A poor candidate for surgery is illustrated in Figure 4.

Occasional patients develop evidence of cardiovascular damage in the stage of intermittent hypertension. In these it seems proper to consider surgical intervention. Thorough denervation of the splanchnic bed by a technic which permits exposure of the kidneys and adrenal glands appears to be the most desirable procedure for most patients. In some, total or subtotal thoracic sympathectomy may prove to be preferable.

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Case Reports

Nephrotic Syndrome Occurring during Tridione Therapy*

HENRY L. BARNETT, M.D., DONALD J. SIMONS, M.D. *and* ROE E. WELLS, JR., M.D.
New York, New York

A RELATIVELY new drug, tridione (3, 5, 5 trimethyloxazolidine, 2-4 dione) has been shown to possess high therapeutic specificity against petit mal seizures.[1] The rare occurrence of serious toxic side effects has also been reported recently.[2] This report concerns a hitherto undescribed renal complication which appears to be related to the administration of tridione.

CASE REPORT

A sixteen year old colored school girl (born April 15, 1931) was first seen at seven and one-half years of age in January, 1939 in the out-patient department of the Children's Clinic of the New York Hospital. The initial complaint was enuresis of one year's duration. Subsequently, her mother described "spells" during which she seemed to be "thinking like dreaming" and as a result stopped whatever she was doing. She became rigid, stared and did not respond to questioning. These episodes lasted about thirty seconds and had been noted for about three months.

No other members of the family were known to have had convulsive disorders or kidney disease. The mother had syphilis and was treated during the pregnancy of the patient.

Physical examination of the patient was unremarkable. She appeared dull and slow. Her intelligence quotient at the age of eight years was 83. Re-examination at the age of eleven, however, cast doubt on the validity of this measurement. At this time she was doing excellent school work and her intelligence quotient was 95. Repeated examinations of the urine showed no abnormalities. A Kline test on the blood and a spinal fluid Wassermann were negative. An electroencephalogram at the age of nine (March, 1940) showed waves strongly suggestive of grand mal epilepsy. A subsequent tracing at the age of ten (January, 1941) showed similar waves plus some dart and dome seizure patterns like those seen in petit mal.

The enuresis subsided after evening fluids were withheld but her "spells" persisted unchanged throughout the period from March, 1940 to October, 1945 despite courses of phenobarbital, benzedrine, dilantin, sodium bromide, ephedrine sulfate, glutamic acid and caffeine citrate given alone and in various combinations. Repeated urine examinations during this period showed no albuminuria or abnormal sediment.

At the age of fourteen years (October, 1945) the patient received tridione. On a dosage of 0.32 Gm. three times daily she continued to have six to seven seizures a day; three weeks following an increase in the dosage to 0.96 Gm. three times a day, the attacks were reduced to one to two a week and they stopped entirely one week later. She remained free from attacks with subsequent reduction in dosage to 0.64 Gm. and later to 0.32 Gm. three times a day; no toxic effects from the tridione were observed.

On June 22, 1946, eight and one-half months following the onset of continuous tridione therapy, pitting edema of the face and legs spontaneously appeared with a gain in weight of 18.2 Kg. over her usual weight of 67 Kg. The blood pressure was 122/70. The urine contained large quantities of protein (3+) and chemical examination of the blood revealed low serum albumin (1.8 Gm./100 ml.) and total protein (3.9 Gm./100 ml.) and elevated serum cholesterol (876 mg./100 ml.). (Fig. 1.)

* From the New York Hospital and the Departments of Pediatrics and Medicine (Neurology), Cornell University Medical College, New York, N. Y.

The red and white blood cell counts, hemoglobin concentration and differential leukocyte count were within normal limits. Tridione was discontinued. On bed rest and low salt and fluid intake, a steady loss of weight followed. By August 1, 1946, five weeks after its appearance, pressure was elevated to 146/84 on this occasion and there was microscopic hematuria. Tridione was discontinued on October 11, 1946. By November 6, 1946, four and one-half weeks after its appearance, the edema had again subsided and the laboratory findings were again

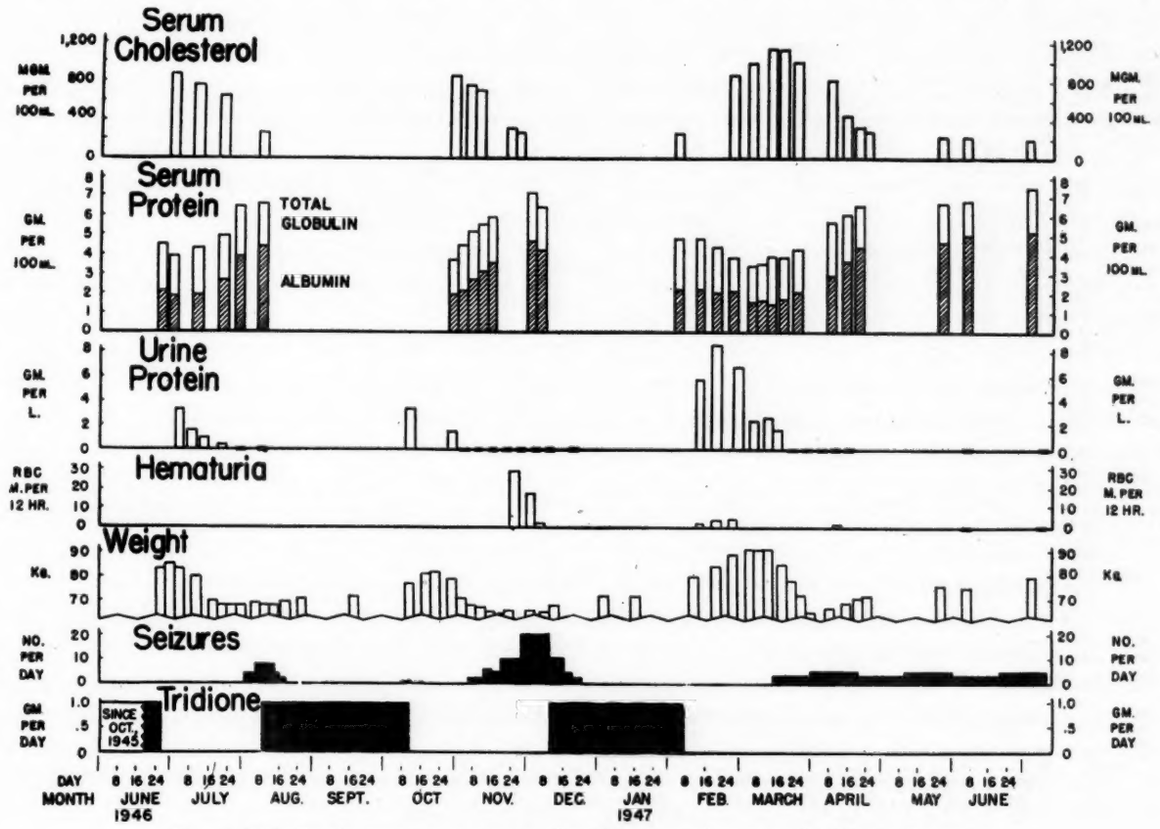

FIG. 1. Relation between occurrence of nephrotic syndrome and tridione therapy.

the edema had subsided and the laboratory findings had returned to within the normal range. At the same time petit mal seizures recurred. Because no other therapy had previously controlled the seizures and because there were no signs of persistent impairment of kidney function, 0.32 Gm. of tridione given three times a day was again started on August 9, 1946, following several test doses without detectable reaction. The frequency of seizures decreased and they stopped entirely ten days later (August 19, 1946). She returned to school.

Following this episode, the patient was free from seizures and her weight remained constant until October 4, 1946; two months after starting tridione the second time, generalized edema was again noted. Physical examination and hematologic and urinary findings paralleled those in the first episode (Fig. 1) except that the blood normal. The seizures, however, recurred and increased in frequency as high as ten to twenty a day. Kidney function tests revealed no decrease in measurable functions. (Table 1.) The increase in severity and frequency of her seizures in the presence of normal renal function prompted the reinstitution of tridione therapy on December 10, 1946, in a dosage of 0.32 Gm. three times a day. Within two weeks her attacks had ceased a third time and she again returned to school and full activity.

On February 7, 1947, two months following resumption of tridione for the third time, edema of the face returned and again tridione was discontinued. Examination again revealed generalized edema, proteinuria, low serum albumin and total protein and high serum cholesterol. (Fig. 1.) The edema was more extensive and persisted longer in this than in the two previous

episodes. In addition there was an elevation of the blood urea nitrogen. (Table 1.) Petit mal seizures appeared on March 14, 1947, five weeks after cessation of tridione, and in this instance antedated subsidence of the edema and proteinuria. The latter cleared on March 25, 1947, five and one-half weeks following the third episode of edema.

Repeated electroencephalograms showed consistent pathologic records strongly suggesting a convulsive disorder. Repeated electrocardiograms were interpreted as normal.

At the time of writing (September 1, 1947), the patient on phenobarbital therapy is having three to five seizures a day but she has completed her school year and has engaged in normal activity. Nephrotic symptoms and signs have been absent for five months.

TABLE 1*

KIDNEY FUNCTION OF PATIENT EXHIBITING NEPHROTIC SYNDROME DURING TRIDIONE THERAPY

Date	Estimated Glomerular Filtration Rate, Mannitol Clearance (C_M) ml./min./1.73 M^2	Effective Renal Plasma Flow Para-Amino Hippurate Clearance (C_{PAH}) ml./min./1.73 M^2	Filtration Fraction C_M/C_{PAH}	Effective Renal Blood Flow $\frac{C_{PAH}}{100\text{-Hematocrit}} \times 100$ ml./min./1.73 M^2	Maximal Tubular Excretory Capacity PAH mg./min./1.73 M^2	Urea Clearance ml./min./ 1.73 M^2	Blood Urea Nitrogen	
							Date	Mg./100 ml.
11-22-46	96.2	490.2	0.197	824.4	93.4	65.2	7-6-46	17.0
	(86.3–101.9)$_{10}$†	(439.3–538.4)$_7$	(0.189–0.203)$_7$	(749.6–900.0)$_7$	(93.1–93.6)$_2$	(61.5–68.9)$_2$	7-11-46	14.0
							7-23-46	16.0
							8-9-46	14.0
							10-29-46	9.0
11-26-46	102.2	542.9	0.188	896.6			11-9-46	11.0
	(91.5–115.3)$_9$	(486.9–595.4)$_9$	(0.174–0.198)$_9$	(798.1–964.7)$_9$			11-12-46	9.5
							11-22-46	7.8
							12-30-46	13.0
							2-14-47	24.4
							2-20-47	31.5
3-24-47	85.2	584.7	0.156	941.6	109.2	51.1	3-6-47	46.9
	(77.3–96.4)$_6$	(504.2–655.5)$_3$	(0.147–0.161)$_3$	(818.3–1052.5)$_3$	(107.3–111.1)$_3$	(51.0–51.1)$_2$	3-12-47	15.2
							3-24-47	8.6
							4-15-47	14.0
							4-21-47	7.8
4-21-47	100.6	567.0	0.191	922.0	95.6	65.7		
	(85.9–108.4)$_6$	(541.4–607.4)$_3$	(0.178–0.198)$_3$	(880.2–987.7)$_3$	(88.9–107.2)$_3$	(63.8–68.6)$_2$		

* The clearances were performed according to the general technic described by Goldring and Chasis, Hypertension and Hypertensive Disease. P. 195. New York, The Commonwealth Fund. 1944.

† (Range of values) Number of periods.

COMMENT

Manifestations of the nephrotic syndrome appeared in this patient during the administration of tridione and disappeared upon withdrawal of the medication on three distinct occasions. Was tridione implicated in this clinical syndrome? Some light may be thrown on this question by an analysis of the symptoms and findings.

Description of Nephrotic Syndrome. The outstanding symptom on the three occasions was generalized pitting edema. The edema was accompanied by proteinuria, hypoproteinemia primarily ascribable to hypoalbuminemia and hypercholesterolemia. In each of the three remissions the proteinuria cleared, the total serum proteins and serum albumin returned to normal limits and the serum cholesterol decreased to normal levels. The results obtained in kidney function tests in two of the remissions (November 22 and 26, 1946 and April 21, 1947) and in one exacerbation (March 24, 1947) and the levels of blood urea nitrogen are shown in Table 1.

Although generalized edema was the outstanding clinical symptom and proteinuria and hypo-albuminemia were the prominent laboratory findings, the hematuria shown in Figure 1 denotes a definite

nephritis. Kidney function tests performed during the periods of remission are considered to be within the normal range. The somewhat abnormal values for mannitol and urea clearances obtained on March 24, 1947 during a period of edema may represent decreased function, especially since during this period the blood urea nitrogen was also elevated and repetition of the clearance tests performed one month later yielded normal values.

The evidence suggests that the disease which occurred during tridione therapy was the nephrotic type of nephritis not associated with persistent impairment of kidney function.

Relation of Tridione Therapy to Nephrotic Syndrome. As shown in Figure 1 the concomitant occurrence of symptoms and tridione therapy is striking. Administration of tridione, of course, could have been coincidental with a spontaneously occurring nephrotic type of nephritis or the medication could have acted only as the agent which precipitated exacerbations of an independent disease. Certainly, numerous factors such as infections, paracenteses and dietary changes among others sometimes alter suddenly, irregularly and inexplicably the course of nephrosis or mixed nephritis in children. Two facts in the present instance are against this interpretation. The regularity of the appearance of symptoms during medication and their subsidence on withholding the drug on three separate occasions certainly contrast with the irregularity of the relationship between the above mentioned factors and the spontaneously occurring disease. Moreover, complete disappearance of albumin from the urine and return of the serum proteins and cholesterol to normal levels on three distinct occasions is certainly not common during remissions of the "natural" disease.

That tridione was causally related to the nephrotic syndrome is suggested by the aforementioned variations from the spontaneously occurring disease and by the striking sequential relation between occurrence of symptoms and therapy. The total picture presented by this patient not only differs from the "natural" disease but is quite unlike that commonly seen with heavy metal poisoning or the toxic nephroses following use of such organic compounds as carbon tetrachloride. The quintad of intense proteinuria associated with hypoproteinemia and generalized edema, of practically normal kidney function and particularly of hypercholesterolemia is relatively rare. This combination of findings associated with drugs is not completely unknown however. So-called "gold nephrosis" has been reported[4–8] in which edema, proteinuria, hypoproteinemia and hypercholesterolemia have been ascribed to the therapy but the same uncertainty concerning pathogenetic relationships existed in these patients. If such compounds as gold salts or tridione are shown to cause the nephrotic syndrome in some patients, an experimental approach to an understanding of the fundamental nature of the syndrome may be provided.

Final evaluation of the relation of tridione to the nephrotic syndrome must await further observations in this and other patients. Similar occurrences in other patients during tridione administration would support a causal relation. In this patient the precipitation of another attack by the administration of tridione after a prolonged remission without the drug would strengthen this thesis. Conversely, a spontaneous exacerbation in the absence of tridione therapy would be evidence for the spontaneous nature of the disease. The absence of recurrences during a prolonged period without tridione would of itself be of no significance since it might occur in either case.

The uncertainty of the rôle of tridione in the causation of a nephrotic type of nephritis in this patient has been emphasized because of the possibility of unfairly incriminating a useful drug. On the other hand, it seems worth while to record the occurrence of the nephrotic syndrome during tridione administration because it is important to call attention to all the

possible toxic effects of a new and widely used medication.

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Primary Systemic Amyloidosis with Nephrosis*

STUART LINDSAY, M.D.

San Francisco, California

PRIMARY systemic amyloidosis is a rare disease with protean manifestations. It is not often recognized during life, probably because it is not generally known that amyloidosis may occur without preceding suppuration.

In general, the sites of amyloid deposition in the primary type of disease are the heart, lungs, skin, striated muscles, mucous membranes and other tissues not usually involved in the more common secondary amyloidosis, although overlapping of the characteristics of the four types (primary, secondary, localized and that associated with multiple myeloma) has often been encountered. Forty-eight cases of primary systemic amyloidosis have been recorded in the literature,[1,2,3,13,14] these have been summarized and the majority tabulated elsewhere.

The present report concerns an additional fatal case of primary systemic amyloidosis in which a nephrotic syndrome was the outstanding clinical feature.

CASE REPORT

S. C., No. U 12,189, a sixty-six year old white widow, was first seen on October 16, 1945. For the previous two years she had been fatigued, felt dizzy and noted increasingly severe constipation associated with rectal bleeding. During this period she had been taking 0.1 Gm. of digitalis daily without significant improvement. Eight months before entry she had had severe pharyngitis with malaise and fever lasting one week. Four months before anorexia and edema of the ankles were noted and during the next four months the level of the edema progressed to the lower thighs. Three months before entry an examination by her physician showed; blood pressure, 104/64 mm. of Hg; urine, specific gravity 1.012, albumin 4 plus, few casts and no red blood cells. There had been no other cardiac or renal symptoms or signs.

The past and family history contained no significant items. Her last menstrual period occurred at the age of fifty-two. There was no subsequent bleeding or vaginal discharge.

The patient was an obese, elderly white woman who was lying flat in bed without apparent distress. She was cooperative but had a poor memory. Her temperature was 36.8°C., pulse 90 per minute, respiration 18 per minute and blood pressure 120/78 mm. of Hg. There was no cyanosis. Slight periorbital edema was noted. The pupils were equal and regular and reacted normally to light and accommodation. The extra-ocular movements were normal. The retinal arteries were moderately sclerotic. Both tympanic membranes were thickened. The nose, mouth and pharynx were normal. The thyroid gland was moderately and symmetrically enlarged. There was an increase in the anteroposterior diameter of the chest. The breasts were senile, atrophic and pendulous. The breath sounds over both lungs were diminished in intensity and bilateral basal râles were heard. The heart was enlarged. The PMI was felt in the fifth left interspace 2 cm. lateral to the midclavicular line. No murmurs were heard. The cardiac sounds were distant but had a good quality. A_2 equaled P_2. The rhythm was regular. The abdomen was obese. There was no shifting dullness. The liver edge could be palpated 6 cm. below the right costal margin. There was slight tenderness over both costovertebral angles. Mild sacral edema was noted. Examination of

* From the Division of Pathology, University of California Medical School, San Francisco, Calif.

the pelvis, rectum and nervous system revealed nothing abnormal. Except for the edema of the legs the extremities were normal.

Examination of the blood on October 16, 1945, give the following data: Hemoglobin 118 per cent (17 Gm.); erythrocytes 5,000,000 per cu. mm.; leukocytes 7,400 per cu. mm.; neutrophilic leukocytes 60 per cent (filamented 55 per cent, nonfilamented 5 per cent); lymphocytes 38 per cent and monocytes 2 per cent. The urine was clear and yellow with a specific gravity of 1.020, albumin 4 plus, no sugar, occasional granular casts, 3 to 4 white blood cells per high power field and no red blood cells present.

Chemical investigation of the blood on October 17, 1945, showed a total serum protein of 4.27 Gm. per cent; albumin 1.9 Gm. per cent; globulin 2.37 Gm. per cent; CO_2 combining power 21.6 mEq./liter; serum chlorides 110.2 mEq./liter; non-protein nitrogen 24 mg. per cent and blood urea nitrogen 12 mg. per cent.

An Addis count done on a twenty-four hour urine specimen on October 19, 1945, showed the following: Volume 1 liter; specific gravity 1.013; pH 7; protein 13.5 Gm. per liter; leukocytes 18,000,000; erythrocytes 1,000,000; casts 500,000, all hyaline. The plasma cholesterol was 384 mg. per cent. Cultures of the urine showed no growth.

The basal metabolic rate on October 23, 1945, was plus 5 per cent. The phenosulfonthalein test gave the following results: twenty minutes, 5 per cent excretion; thirty minutes, 35 per cent excretion; sixty minutes, 15 per cent excretion; ninety minutes, 10 per cent excretion; a 65 per cent total excretion.

The rose bengal hepatic function test showed 61 per cent retention of the dye in eight minutes and 42 per cent retention in fifteen minutes. Kolmer and Kline tests of the blood were negative.

An electrocardiogram showed an abnormal record of no characteristic pattern, suggesting myocardial disease. There was moderate left axis deviation and low voltage. There also were slightly depressed S-T segments in leads I and IV, diphasic T_1 and low T_4. Roentgenograms of the chest revealed elongation and widening of the aorta, fibrosis at the right apex and bilateral basal pleural thickening.

Her clinical course while in the hospital was afebrile. There was a weight loss of 6.4 Kg. and almost complete disappearance of the edema. She was given a diet containing 50 Gm. of protein and less than 2 Gm. of sodium chloride per day. The clinical diagnosis was chronic glomerulonephritis (nephrotic stage).

The patient entered the hospital again on November 24, 1945. With unrestricted activity at home her legs again became edematous, in spite of a salt-free diet. Constipation and rectal discomfort continued. On November 17, 1945, she awakened with a mild chill, slight dyspnea, a temperature of 39.5°C. and a gradual onset of severe pain in the anterior right thorax. The symptoms were accompanied shortly by a mild, dry, non-productive cough. After two and one-half days of sulfanilamide therapy the fever subsided, but the orthopnea, dyspnea and cough persisted.

The physical examination revealed that the patient was apprehensive, slightly cyanotic, very orthopneic but alert and cooperative. Her temperature was 37.8°C., pulse 100 per minute, respirations 30 per minute and blood pressure 115/70 mm. of Hg. There was moderate pitting edema of both ankles. The periorbital edema was still present. There was slight redness of the posterior pharynx. The trachea was deviated to the right. There was symmetrical enlargement of the thyroid gland. Expansion of the chest was limited. There were physical signs of bilateral pleural effusion, from the sixth interspace downward on the right and the eighth interspace downward on the left. Generalized rhonchi and moist râles were heard in the upper pulmonary fields, both anteriorly and posteriorly. The point of maximum cardiac impulse was not palpable. The heart was enlarged 4 cm. to the left of the midclavicular line in the fifth interspace; the position of the right border could not be ascertained. There was a split M_1. A_2 equaled P_2. The cardiac sounds were distant and of poor quality. There were no murmurs. There was mild pitting edema of the abdominal walls. The edge of the liver extended 5 cm. below the right costal margin and was not tender. Examination of the remainder of the

abdomen, back, rectum and genitalia showed nothing abnormal. The legs were grossly edematous.

Examination of the blood gave the following data: Hemoglobin 106 per cent (15.5 Gm.); leukocytes 10,600 per cu. mm.; neutrophilic leukocytes 76 per cent (filamented 61 per cent, non-filamented 15 per cent); eosinophilic leukocytes 2 per cent; lymphocytes 14 per cent; monocytes 8 per cent; uncorrected sedimentation rate 9 mm.; packed cell volume 50 and corrected sedimentation rate 16 mm. The urine was orange and turbid, pH 7.5, specific gravity 1.027, albumin 4 plus, sugar-green reduction, 5 hyaline casts, 2 granular casts, 8 waxy casts and 1 broad cast per slide; 120 leukocytes per high power field with no red blood cells present. Many additional urine specimens examined during the next six weeks gave similar findings. The feces contained 1 plus occult blood. The venous pressure was 8.2 cm. of saline. The arm to tongue circulation time (decholin) was 14 seconds.

Roentgenograms of the chest on November 25, 1945, showed moderate, bilateral pleural effusion extending to the third interspaces anteriorly. The visible portions of the lungs were clear except for the previously noted fibrosis at the right apex. There was slight displacement of the mediastinum to the right. Cultures of the blood showed only contaminating diphtheroids in forty-eight hours.

Right thoracentesis yielded dark, sanguineous fluid with a specific gravity of 1.010, 3,000 red blood cells per cu. mm., 2,300 leukocytes per cu. mm, lymphocytes 37 per cent and neutrophilic leukocytes 67 per cent. Culture of the fluid showed no growth and no acid-fast organisms could be demonstrated by guinea pig inoculation.

Chemical examination of the blood on November 26, 1945, showed the following: Nonprotein nitrogen 35 mg. per cent; total serum protein 5.0 Gm. per cent; albumin 2.1 Gm. per cent; globulin 2.9 Gm. per cent; CO_2 combining power 25.1 mEq./liter; serum chlorides, 98.4 mEq./liter. On December 3, 1945, the nonprotein nitrogen level of the blood was 35 mg. per cent, the CO_2 combining power, 24.7 mEq./liter and the serum chlorides, 105.6 mEq./liter. Cultures of the sputum showed the predominant organisms to be Streptococcus viridans and non-hemolytic Staphylococcus albus.

On November 28, 1945, examination of the blood gave the following data: Hemoglobin 100 per cent (14.5 Gm.); leukocytes 16,400 per cu. mm.; neutrophilic leukocytes 82 per cent (filamented 54 per cent, non-filamented 28 per cent); lymphocytes 10 per cent and monocytes 8 per cent.

No acid-fast organisms were demonstrated in the sputum by repeated smears and guinea pig inoculation. Cultures of the blood showed no growth. There were no pneumococci in the sputum.

An electrocardiogram on November 30, 1945, showed the following: Rate 125; sinus tachycardia; P-R 0.18 sec.; low voltage QRS complex; slight left axis deviation; flat T waves in all leads and low R_4.

On December 10, 1945, examination of the blood showed the following: Hemoglobin 84 per cent (12.3 Gm.); erythrocytes, 3.7 million per cu. mm.; leukocytes 9,200 per cu. mm.; neutrophilic leukocytes 82 per cent (filamented 56 per cent, non-filamented 26 per cent); lymphocytes 15 per cent and monocytes 3 per cent.

An additional roentgenogram of the chest on January 4, 1946, showed less extensive pleural effusion than previously. There was a 2 cm. rounded density superimposed upon the shadow of the right fifth rib anteriorly. There was bilateral basal pleural thickening.

From November 24, 1945 until December 11, 1945, the patient's temperature ranged between 38° and 39°C., and from December 11th to December 17, 1945, it was normal. For the next six days it remained elevated between 37.5° and 38°C. and was normal thereafter until the time of death. It was felt that there was a bilateral pneumonitis underlying the bilateral pleural effusion. A salt-free diet, which contained 80 Gm. of protein, was fed to her. Oxygen was administered continuously through a B.L.B. mask at the rate of 8 liters per minute. Fifty thousand units of penicillin were given intramuscularly every four hours and 200,000 units were administered intravenously on several occasions. Large quantities of plasma, ordinarily

500 cc. per day, were given between November 29th and December 17, 1945. This was given primarily to combat the lowered blood pressure which rarely was above 85 mm. of Hg systolic. Several transfusions of whole blood were administered during this period. Mercurial diuretics and digitalis were given intermittently.

Because no response to this regimen was apparent by December 18, 1945, and because the patient's status seemed hopeless, all therapy was discontinued and only morphine for discomfort and ammonium chloride to produce diuresis were given. During the next three weeks there was an apparent complete clearing of the pneumonic process. The blood pressure remained below 90 mm. Hg systolic. Throughout the illness the patient was anorexic and her intake of protein was far below the prescribed amount.

On January 12, 1946, the patient climbed over the side rail of the bed and fell to the floor. There was no evidence of injury but later during the day her temperature suddenly became elevated to 38°C., coarse tracheal rhonchi appeared the pulse rate rose to 144, the patient became extremely dyspneic and cyanotic and expired within a few hours.

The autopsy (UA.46:6) was performed four and one-half hours after death. The body was extremely obese and there was massive edema of the subcutaneous tissues, especially in the lower extremities. The head, eyes, ears, nose and mouth were not grossly altered. One to 2 mm., slightly elevated, brown, macular and reddish angiomatous lesions were present on both forearms. The peritoneal cavity was normal and did not contain an excessive amount of fluid. The liver edge lay between 2 and 4 cm. below the costal margins and the xiphoid process.

The right pleural cavity contained approximately 3,000 cc. of clear yellow fluid and clotted fibrin. About 1,000 cc. of similar material were present in the left pleural cavity. There were both fibrous and fibrinous pleural adhesions at the apices and the bases. No thymic glandular tissue was evident. The pericardial cavity contained 100 cc. of clear fluid and there was no alteration of the pericardial surfaces.

The heart weighed 360 Gm. It had a smooth, glistening visceral pericardium which contained a normal amount of fat. The ventricular myocardium, especially on the left side, was firm and had a pale yellowish-tan color. Throughout the left ventricular wall, especially near the apex, narrow, fine, grayish, translucent streaks were visible between the muscular bundles. This material stained a deep mahogany brown with a strong solution of iodine, U.S.P. The left ventricle averaged 1.5 cm. in thickness and the right ventricle 0.5 cm. in thickness. The left auricular wall was thickened, measured 3 mm. in thickness and had a leathery consistency. The right auricular wall averaged only 1 mm. in thickness and was of normal consistency. The left ventricular endocardium was normal. The endocardium of both auricles was studded with tiny, 0.5 mm., slightly elevated, rounded, translucent, grayish nodules. Several 2 mm., pale, yellow, fibrous nodules were noted in the endocardium of the right ventricle. The aortic and mitral valves contained small, yellow, atheromatous plaques. Approximately 0.5 cm. from the free edge of the left leaflet of the tricuspid valve was a subendothelial, translucent, ovoid nodule measuring 0.5 cm. in diameter. The valves measured as follows: AV 7.5 cm., MV 10 cm., PV 8 cm. and TV 12.5 cm. There was no gross alteration of the coronary arteries; the coronary ostia were patent. Moderate dilatation of the right side of the heart, especially of the right auricle, was present. A large, firmly adherent, dry, friable, antemortem thrombus was found in the right auricular appendage.

The right lung weighed 540 Gm. and the left lung 480 Gm. The mucosa of the major and smaller bronchi was congested. There were scattered yellowish opaque, atheromatous plaques in the intima of the major branches of the pulmonary artery. Several of these arterial branches contained adherent, dry, firm, twisted, antemortem thrombi. Both lungs were diffusely congested and edematous. Posteriorly and inferiorly they were partially atelectatic, the result of pressure by the pleural fluid. Two wedge-shaped infarcts, measuring 3 and 5 cm. in diameter respectively, were found in the lower and lateral portions of the lower lobe of the left lung. The larger was of more recent origin and had a reddish wet surface; the smaller was pale and firm. The main pulmonary artery of the lower lobe of the left lung was completely

obstructed by an antemortem thrombus. In the lower lobe of the right lung and in the apex of the right lung similar 3 to 4 cm., triangular-shaped infarcts were demonstrated. The pleural surfaces were smooth and glistening. The hilar lymph nodes showed nothing abnormal.

The liver weighed 1,480 Gm., and was normal in size and appearance. No amyloid could be demonstrated by staining with a strong solution of iodine, U.S.P. There was mild thickening of the wall of the gallbladder and the lumen contained several facetted 1.5 cm. cholesterol stones. A similar stone was found in the cecal lumen. The extrahepatic bile ducts and pancreas were normal. The spleen weighed 120 Gm. Its capsule was smooth. The cut surface had a deep red color and a fibrous, dry consistency. The gastroenteric tract had a grossly normal appearance throughout its extent. The mesenteric and preaortic lymph nodes were small. The adrenal glands were of normal size; an occasional adenomatous nodule was noted in the cortical layers.

The right kidney weighed 240 Gm., and the left 250 Gm. The blood vessels of the renal pedicles were normal. The capsules were slightly adherent and the subcapsular surfaces were finely granular, pitted and pale yellow in color. On the cut surfaces the cortical layers appeared pale and yellow in color. They were soft, opaque and striated; the demarcation from the deep red medullas was less distinct than normal. Punctate, deep brown spots appeared throughout the cortical layers when the tissue was stained with a strong solution of iodine, U.S.P., indicating the presence of amyloid substance in the glomeruli. There was slight dilatation of the renal pelves and a few small petechial mucosal hemorrhages were observed. The ureters and bladder were normal. The internal genitalia were atrophic but otherwise not unusual. Minimal atherosclerosis was evident in the aorta. The thyroid gland was moderately enlarged; its substance had a normal color and consistency. On the posterior capsule of the thyroid gland four parathyroid glands were found; these were enlarged approximately two to three times. The brain weighed 1,240 Gm. The meninges were grossly normal. The external blood vessels showed no thickening of their walls. Both externally and on section the cerebral hemispheres, the cerebellum and the brain stem were entirely normal. The pituitary gland was of normal size.

Microscopically all portions of the examined myocardium were distinctly altered. There was extensive interstitial and pericellular deposition of hyaline, eosinophilic material which stained specifically for amyloid substance with the Congo red and crystal violet stains. (Fig. 1.) The pericellular amyloid formed an imprisoning sheath or ring about the individual muscle fibers. Where the rings were thicker and the interstitial amyloid most abundant the myocardial fibers were atrophied or completely absent. Other muscle cells showed degenerative changes with vacuolization and deposition of pigment granules. In most myocardial regions the fibers appeared essentially normal, even though all were surrounded by amyloid rings of varying thicknesses. Narrow amyloid deposits also surrounded the individual fat cells of the epicardial layer. The amount of subendothelial endocardial amyloid varied in different portions of the heart. It was most abundant in the right auricular wall where the material often projected into the cardiac lumen. Here it was generally covered by an endothelial layer. In the right auricle an organizing antemortem thrombus lay immediately adjacent to the large, endocardial amyloid deposits. Almost all the blood vessels of the heart, including arteries, veins and capillaries, contained small, subendothelial, rounded, irregular, amyloid deposits. None of these seriously narrowed the lumen of these vessels. All of the cardiac valves contained small, deep, interstitial, amyloid deposits; this material formed the translucent nodule seen in the tricuspid valve.

Almost all the pulmonary arteries, veins and arterioles contained amyloid deposits in their walls. The branch of the pulmonary artery leading to the lower lobe of the left lung contained large, irregular amyloid clumps, chiefly in a subendothelial situation. The lumen of this vessel was largely occluded by a well organized thrombotic mass. In other large pulmonary arteries where the amyloid was less abundant, thrombi of more recent origin without organization were noted. In the smaller vessels containing the most abundant amyloid thrombosis had also

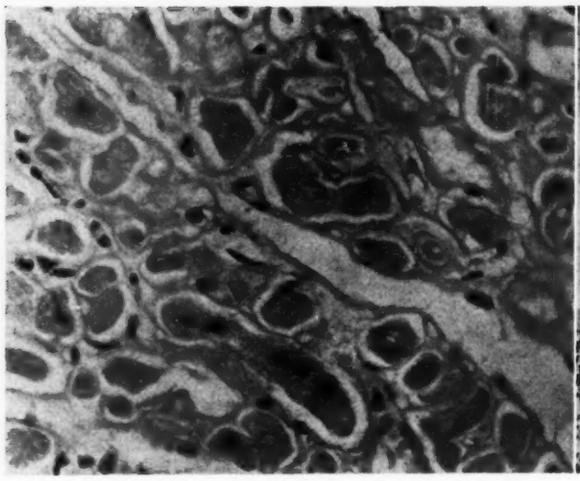

FIG. 1. Pericellular amyloid infiltration in the myocardium; hematoxylin and eosin × 500.

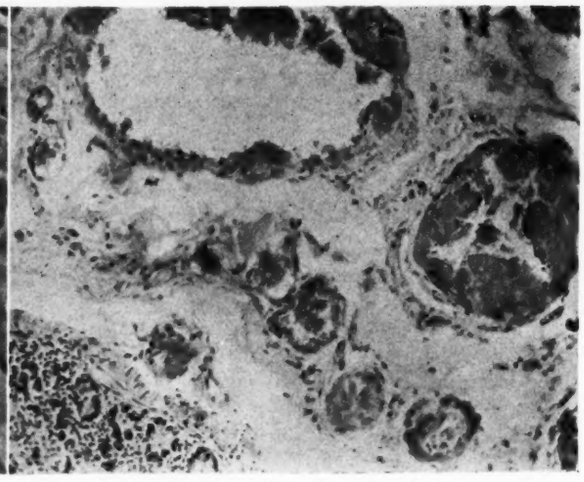

FIG. 2. Amyloid infiltration of duodenal blood vessels; hematoxylin and eosin × 120.

occurred. Almost all the alveolar walls were thickened as the result of amyloid deposition about the capillaries of the alveolar walls. The pulmonary infarcts were hemorrhagic and showed varying degrees of surrounding inflammatory reaction and organization. Adjacent to the infarcts the vascular amyloid infiltration, thrombosis and vascular obstruction were greater than elsewhere. In the pulmonary parenchyma the small bronchi and bronchioles contained purulent exudate.

The hepatic parenchyma was essentially normal except for mild congestion of the central sinusoids. Subendothelial amyloid deposits were observed in almost all the small hepatic arteries. There was lymphoid atrophy of the spleen. The central arteries and arterioles were thickened and hyalinized but only a few contained amyloid material. The splenic pulp was fibrotic and the reticuloendothelial cells often contained brown pigment. Except for one small zone of interstitial fibrosis the pancreatic parenchyma was normal. A small number of the arterioles contained subendothelial amyloid deposits. Similar vascular deposits were present in the wall of the gallbladder.

All portions of the gastroenteric tract showed a similar histologic alteration. There were extensive amyloid deposits in the walls of the mucosal and submucosal blood vessels, including arteries, veins and capillaries. (Fig. 2.) Pericellular amyloid deposits were observed about the individual smooth muscle cells and also surrounding the fat cells of the subserosal layer. The most extensive muscular involvement was in the muscularis mucosa. The largest amyloid deposits were in the stomach and duodenum, with considerably less in other portions of the gastroenteric tract. The cellular layers of the adrenal glands were not significantly altered, although there were small masses of amyloid material in the walls of the smaller capsular vessels and about the fat cells in the periadrenal tissues.

With few exceptions the renal glomeruli contained pericapillary amyloid deposits. (Fig. 3.) Almost all the glomerular capillaries were narrowed but only a few glomeruli had been completely replaced by amyloid substance. The endothelial and epithelial cells of the damaged glomeruli were compressed and atrophic; there was no cellular proliferation. In most of the glomeruli, Bowman's capsule was thin and normal; in a few, the capsule showed a fibrous or amyloid thickening. Some afferent arterioles contained subendothelial amyloid deposits while some were occluded by this process. The tubules were severely damaged, especially those of the convoluted group. Many were dilated and nearly all contained hyaline casts. There was considerable cellular swelling; lipid droplets were often encountered in the degenerating cells. Capillary amyloid infiltration outside of the glomeruli was not demonstrated but there were many small interstitial amyloid deposits in the cortical layers. Small accumulations of

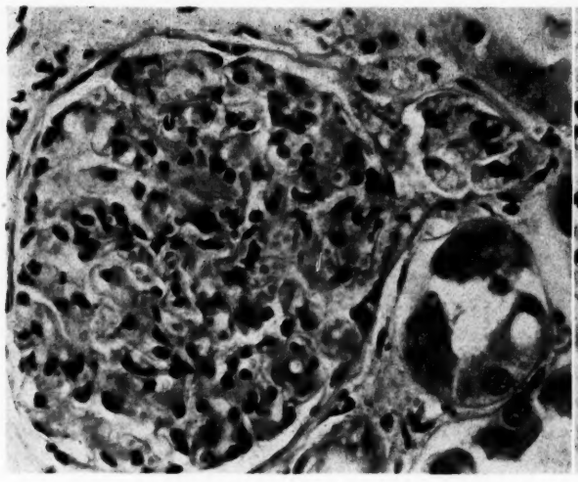

FIG. 3. Glomerular amyloid infiltration; hematoxylin and eosin × 500.

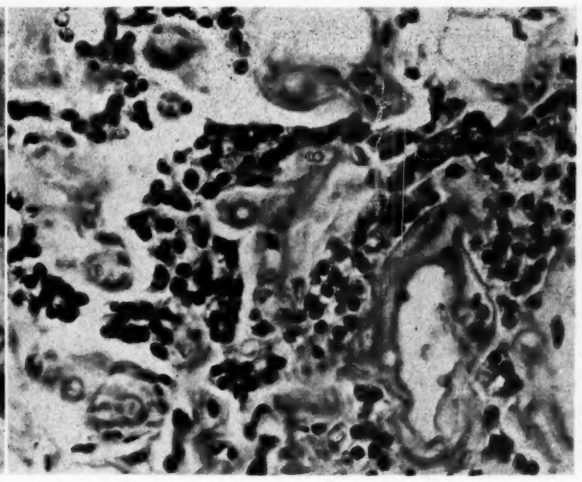

FIG. 4. Parathyroid amyloid infiltration; hematoxylin and eosin × 500.

interstitial lymphocytes and zones of scarring were scattered throughout the cortical layers and were most numerous in areas where the amyloid infiltration was greatest. The small vessels in the medulla and pelvic tissues contained subendothelial amyloid deposits. The arcuate arteries showed only minimal amyloid infiltration. The pelvic submucosa was edematous and showed small hemorrhages and lymphocytic collections.

The layers of the bladder were normal but almost all the arterioles contained amyloid masses. The internal genitalia were atrophic but not otherwise unusual. Only a few of the small ovarian and tubal blood vessels contained amyloid deposits. There was atrophy of the breast parenchyma. Small amounts of capillary amyloid were present in the pituitary gland. The thyroid acini were slightly reduced in size, were lined by tall cuboidal epithelium and were filled with evenly staining colloid which was vacuolated at the margins. There was amyloid infiltration of the walls of the small thyroid arteries and about the fat cells near the capsule. Even though the parathyroid glands were enlarged there was no cellular hyperplasia. The increase in size was the result of extensive amyloid deposition in the interstitial connective tissues surrounding the individual stromal fat cells. (Fig. 4.) Compression and destruction of some of the glandular tissue had occurred. A few small, typical atheromatous plaques were noted in the aortic intima. The media was not altered. There were a few small vessels in the adventitial layer which were infiltrated with amyloid material. All the lymph nodes had a normal histologic appearance and contained no amyloid. There were only a few small interstitial masses of amyloid substance present in the dermal layer of the skin. The bone marrow showed a normal cellular distribution; amyloid material and plasma cells were absent. The central nervous system had an entirely normal microscopic appearance and contained no demonstrable amyloid material.

COMMENTS

In secondary amyloidosis the kidney is a common site of amyloid deposition. The variability of the manifestations of renal amyloidosis depends upon the amount and extent of the amyloid infiltration.[4] Minimal amounts of glomerular amyloid produce insufficient injury to cause albuminuria. With larger amounts of glomerular amyloid there is a more severe glomerular injury which is then associated with albuminuria. This may lead to hypoproteinemia, lowering of the osmotic pressure of the plasma and generalized edema. With still greater glomerular, vascular and interstitial amyloid deposition, renal insufficiency, at times associated with hypertension, follows. It is apparent that amyloid nephrosis is a type of moderately advanced renal amyloidosis

and that the lipid degenerative changes in the tubules are the result of diminution of glomerular blood flow.[5]

Of the forty-eight recorded cases of primary systemic amyloidosis twenty-five had some degree of renal amyloidosis. In the majority of these there was minimal glomerular or vascular amyloid infiltration, associated in a few instances with albuminuria as the only manifestation. In three patients there was a progressive, fatal azotemia.[6,7,8] In Gerber's case[9] a nephrotic syndrome, associated with hypercholesterolemia, normal renal function, albuminuria, a positive Congo red test and normal blood pressure, persisted for over two years and was followed by renal insufficiency and hypertension, the result of increasing amyloid infiltration of the kidneys. In an additional case recorded by Christian,[10] and later by Dillon and Evans,[11] a typical nephrotic syndrome[12] was the outstanding manifestation of amyloidosis of the primary type.

SUMMARY

A fatal case of primary systemic amyloidosis is reported. The patient was a sixty-six year old woman who presented the clinical and laboratory signs of nephrosis. Widespread amyloid infiltration was demonstrated at autopsy and renal amyloidosis accounted for the nephrotic syndrome.

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Special Feature

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE MIDWESTERN SECTIONAL MEETING
HELD IN CHICAGO, OCTOBER 30, 1947

GLUTAMIC ACID AND VOMITING IN DOGS: A COMPARISON OF ITS ADMINISTRATION INTO THE PORTAL SYSTEM AND EXTREMITY VEINS. *A. G. Lasichak, M.D.* and *S. Levy, Ph.D. (by invitation), Eloise, Michigan.* (From the Wayne County General Hospital.)

It has been shown that the intravenous administration of glutamic acid may produce nausea and vomiting in both man and animals. However, large amounts of glutamic acid may be taken orally without producing these reactions. This difference may be due to the rôle of the liver in detoxifying the orally administered glutamic acid. In this study two routes were used for infusion into the portal system: the intrasplenic route and direct injection into the portal vein. The first method was achieved by transplanting the spleen subcutaneously in five dogs and administering the solution of glutamic acid directly into the spleen by means of a needle. Direct infusion into the portal vein was accomplished by using a modified London angiostomy technic in two dogs. All animals received an infusion of 1.4 Gm. of glutamic acid and 0.4 Gm. of sodium bicarbonate per 100 ml. The solution was injected at a constant rate until vomiting occurred, and the volume necessary to produce vomiting was used as an index of tolerance. In all of the twenty-six tests carried out the amount of glutamic acid infused intraportally exceeded the amount given intravenously for any given animal. The blood amino acid nitrogen and urea plus ammonia nitrogen were determined. No striking differences were found. The results indicate that intraportal administration of glutamic acid is better tolerated than the intravenous route because of detoxification by passage through the liver.

RENAL FUNCTION IN GENERAL ANESTHESIA: A CLINICAL STUDY OF CHLOROFORM. *E. B. Cohen, M.D., Madison, Wisconsin.* (From the Departments of Medicine and Anesthesiology, University of Wisconsin Medical School.)

Eighty patients subjected to major surgical procedures were studied before and after operation. In forty instances the anesthetic agent was chloroform, and in forty cases a general anesthetic agent other than chloroform was used. These control cases were: ether, twenty; cyclopropane, seven; tribromethanol, seven; vinethene, six. Anesthesia was of long duration averaging two hours for both the chloroform and the control groups. The operations performed were all extensive. There were no important differences in sex incidence or age distribution.

Over 200 urea clearance and PSP excretion tests and a larger number of NPN determinations and urinalyses were done in the early postoperative period. No significant differences in renal function between the forty chloroform and forty control cases were observed. Similarly, serial postoperative blood sugar and alkali reserve determinations showed no notable differences between the chloroform and control groups.

It is suggested that the postoperative derangements of homeostasis and renal function often attributed to the toxic effects of anesthetic drugs on the kidney are actually extrarenal in origin. The uniformity of apparent depression of renal function which we have observed regardless of the agent used would support this conclusion

TRANSPORT AND EXCRETION OF URIC ACID IN MAN. III. PHYSIOLOGIC SIGNIFICANCE OF THE URICOSURIC EFFECT OF CARONAMIDE. *W. Q. Wolfson, M.D., C. Cohn, M.D., R. Levine, M.D.* and *B. Huddlestun, M.D.* (*by invitation*), *Chicago, Illinois.* (From the Departments of Biochemistry and Metabolic and Endocrine Research, Medical Research Institute, Michael Reese Hospital.)

In normal adults following oral administration of a single 4.6 Gm. dose of caronamide the true urate excretion increases from 50 to 120 per cent within two hours. Simultaneously the plasma urate falls slightly and the urate clearance increases to about twice its original value. The glomerular filtration rate remains at about the fasting value.

This effect is similar to that produced by other drugs (cinchophen, salicylate, diodrast, salyrgan) all of which produce a simultaneous increase in minute excretion of urate and a decrease in plasma urate concentration. This pattern of pharmacologic actions has been termed the "uricosuric effect."

Most previous workers believed the uricosuric effect to be due to inhibition of tubular reabsorption of urate but a number of considerations indicate that this is improbable. Both caronamide and benzoate block the tubular excretion of penicillin; yet caronamide has a uricosuric effect while benzoate has precisely the opposite effect upon urate excretion. Both sorbitol and mannitol are cleared at the glomerular filtration rate; but sorbitol gives a striking uricosuric effect while its stereoisomer, mannitol, does not. Certain other substances which produce the uricosuric effect are effective in such small amounts that it is difficult to believe their action to be due to direct blocking of a tubular reabsorptive mechanism. A list of more than forty uricosuric agents which we have compiled includes substances excreted by filtration and reabsorption, by filtration and tubular excretion, and by filtration alone. Such diversity of excretory mechanisms makes it improbable that all share the ability to block the reabsorption of urate by the tubules.

Elsewhere we have presented data which indicate that there is normally little or no tubular reabsorption of urate. All of the urate passing the glomerulus appears to be excreted in the urine, with the possible exception of a small fraction undergoing back-diffusion. This appears to depend upon the fact that only a small proportion of the plasma urate is freely diffusible through the human glomerulus. The action of caronamide, and possibly that of the other uricosuric drugs, may be understood by postulating that such agents increase the fraction of the plasma urate which passes the glomerular filter.

OCCURRENCE OF GASTRIC NEOPLASMS IN YOUTH. *M. Block, M.D., A. H. Griep, M.D.* (by invitation) and *H. M. Pollard, M.D., Ann Arbor, Michigan.* (From the Department of Internal Medicine, University of Michigan.)

The primary obstacle to making a diagnosis of carcinoma of the stomach in youth appears to be the patient's age. Since only limited information is available, it was believed that the usual clinical dictum that a gastric lesion in a patient below the age of thirty-one is probably benign was not necessarily justified.

In a study of this problem the following information was obtained: (1) A survey of the occurrence of carcinoma of the stomach during a twenty-year period (1925 to 1945) at the University Hospital revealed that there were 1,913 carcinomas in a total of 453,400 registrations. This is an incidence of 0.42 percent. (2) Of the 1,913 carcinomas during this period, twenty cases occurred in patients below the age of thirty-one (an incidence of 1.04 per cent of all gastric carcinomas seen). Seventeen of these twenty cases had metastases when first examined, and the diagnosis of carcinoma was usually delayed because benign gastric ulcer was generally considered in view of the patient's youth. (3) During the same twenty-year period, fifty-three other gastric lesions occurred in the same age group (fifty benign gastric ulcers, two gastric lymphoblastomas and one gastric lues). (4) These figures demonstrate that all gastric lesions are rare in patients below the age of thirty-one, but when a gastric lesion does occur, the probability of its being neoplastic is at least 30 per cent.

HEMOCHROMATOSIS WITH APLASTIC ANEMIA. *F. R. Schemm, M.D., E. Hildebrand, M.D.* (*by invitation*), *F. H. Crago, M.D.* (*by invitation*) and *J. A. Layne, M.D., Great Falls, Montana.* (From the Departments of Medicine and Pathology, Great Falls Clinic.)

Severe anemia is an uncommon finding in hemochromatosis. However, several cases of aplastic anemia accompanying hemochromatosis have been reported. We have observed a fifty year old man whose principal complaint was weakness. Physical examination was essentially normal. Examination of the blood revealed a slight anemia and leukopenia, a prolonged bleeding time and a complete lack of clot retraction at forty-eight hours. The bone marrow was found to be active and the proportion of cells normal. There was no hematologic response to iron or liver therapy. The erythrocyte and leukocyte counts gradually declined. A diagnosis of primary splenic neutropenia was entertained and splenectomy was performed. A histopathologic diagnosis of hemochromatosis was made. The patient failed to respond clinically and the hemotologic findings remained unchanged. Repeated blood transfusions were necessary to maintain life. Glycosuria was never demonstrated but the glucose tolerance curve was elevated. About four years after onset of symptoms the patient died. Necropsy revealed iron pigment in most of the parenchymatous organs except the pancreas.

This man was continuously employed for many years in a copper refinery. Mallory and others have drawn attention to the association of hemochromatosis with exposure to copper. This case supports this concept.

Quantitative Estimation of Sternal Bone Marrow Activity in Pernicious Anemia.

A. S. Weisberger, M.D. (by invitation) and *R. W. Heinle, M.D., Cleveland, Ohio.* (From the Department of Medicine, School of Medicine, Western Reserve University.)

Estimation of the activity of the sternal marrow based upon the values of the nucleated cell count, myeloid-erythroid volume and fat content obtained from 1.0 ml. of aspirated material is frequently unreliable. When these values are compared with the actual histologic appearance of the marrow, wide discrepancies are sometimes encountered. This is especially true in cases in which the bone marrow is composed of densely packed cohesive cells, as in pernicious anemia in relapse.

In this study the histologic appearance of the sternal marrow was compared with the values for the nucleated cell count and volumetric pattern obtained from 1.0 ml. of aspirated material in cases of pernicious anemia. Histologic sections of marrow particles, the nucleated cell count and the volumetric pattern were all obtained from the same sample.

In most patients with pernicious anemia in relapse, low values were obtained for the nucleated cell count and myeloid-erythroid volume, indicating normal or decreased activity. However, the histologic sections revealed densely packed, markedly hyperactive marrow. In the cases of treated pernicious anemia the values for the nucleated cell count and myeloid-erythroid volume were within normal limits and the histologic sections showed normal cellular activity.

The lack of correlation between the nucleated cell count, myeloid-erythroid volume and histologic appearance in cases of pernicious anemia in relapse is thought to be due to the density and cohesiveness of the marrow which resists separation on aspiration.

Absorption and Excretion of Chorionic Gonadotrophin.

W. E. Brown, M.D. and *J. T. Bradbury, Sc.D. (by invitation), Iowa City, Iowa.* (From the Department of Obstetrics and Gynecology, University of Iowa.)

Human chorionic gonadotrophin has been shown to have a luteotrophic function in the woman. In appropriate dosage it will induce a pseudopregnancy as demonstrated by a delay in menses, persistence of pregnandiol excretion, prolongation of the life of the corpus luteum, decidual changes in the endometrium and a positive Aschheim-Zondek reaction. Five thousand I. U. daily was shown to be a minimum effective dose when the hormone was given intramuscularly in aqueous solution.

Because of the cost and difficulty in preparing a pyrogen-free material for intramuscular use, studies were undertaken to find alternate methods for administering this hormone. Chorionic gonadotrophin was given by various routes to a series of women in doses ranging from 2,500 to 1,000,000 I.U. Urinary excretion of chorionic hormone was determined by the Aschheim-Zondek reaction in rats.

After intramuscular injection of 10,000 I. U. of gonadotrophin the hormone appeared in the urine in such quantities that it could be demonstrated in urine volumes equivalent to a three-minute output. Excretion occurred in the first

six hours after administration in aqueous solution. When injected in a wax and oil medium the rise in urinary levels was delayed about eighteen hours. Consistently positive Aschheim-Zondek tests were not obtained with three-minute urine volumes later than thirty hours after an aqueous solution was given, whereas the tests were positive forty-eight hours after the wax preparation was injected. When the hormone was given as an emulsion, the urinary excretion findings indicated only a slight delay in initial absorption and persistence through the forty-eight-hour test period.

When given orally in plain or salol-coated capsules in doses as high as 200,000 I.U., the hormone was not excreted in detectable amounts. When a Miller-Abbott tube was passed into the ileum and 300,000 I.U. of hormone was introduced, even a three-hour urine volume did not contain any trace of hormone, and increasing the dose to 1,050,000 I. U. resulted in only a trace of hormone in a three-hour urine volume. Similarly, 123,000 I. U. introduced as a retention enema was followed by the appearance of only a small amount in the urine. From these experiments it is obvious that enteral administration is not feasible due to the destruction of the hormone in the gastrointestinal tract.

EFFECT ON FETAL RESPIRATION OF METHIDON ADMINISTERED DURING LABOR. *A. C. Barnes, M.D.* and *(by invitation) F. B. Hapke, M.D., Columbus, Ohio.* (From the Ohio State University Medical School.)

The present study is concerned with the respiratory depressant effects on the fetus of methidon administered to the mother during labor.

Ninety patients have been delivered under low spinal or caudal anesthesia. No drugs other than the ones under study were administered systemically. The times of the first fetal respiration and of the first lusty cry were clocked for each delivery. Thirty patients served as a control group and received no systemic medications. Thirty patients received methidon at varying intervals prior to delivery. Thirty patients received demerol to serve as additional controls.

On the basis of these studies we believe that: (1) The experimental method used here offers the most valid approach to the study of neonatal narcosis available to date. (2) Regardless of time intervals prior to delivery, 10 mg. of methidon is without significant effect on fetal respiration. (3) A 15 mg. dose of methidon, if administered three hours or less before delivery, produces a significant delay in the first respiration and first lusty cry. If the time interval is greater than three hours, little depressant effect could be noted. (4) Methidon administered under these circumstances is a more marked respiratory depressant than demerol.

EFFECT OF GERMAN MEASLES DURING PREGNANCY. *Stuart Abel, M.D. (by invitation)* and *T. R. Van Dellen, M.D., Chicago, Illinois.*

A request for letters from mothers who had had German measles during pregnancy was included in a syndicated health column. They were asked to state the exact month of gestation that the illness occurred and the effect on the offspring. Over ninety replies were obtained and of these, eighty-two were considered acceptable. The series includes two sets of twins, making a total of eighty-four children.

Three stillbirths were recorded from mothers having German measles during the first trimester of pregnancy. Twenty-five of the children were normal at birth. In seven of these the mother contracted the disease during the first trimester, eleven during the second and seven in the last. Fifty-six of the infants were abnormal at birth, thirty-six with a single defect and twenty with more than one defect. In forty-four (76 per cent) of these, the mother told of having German measles during the first trimester of pregnancy, eight in the second, one in the third and unknown in three. Nineteen of the infants had congenital heart disease, seventeen had cataracts, fourteen were deaf, and seven were mentally deficient. Gastrointestinal, eye, spinal and skeletal abnormalities also occurred in lesser numbers.

The most serious defects or combination of defects occur in women having German measles during the first trimester; defects are less serious and more infrequent in the second. Only one abnormal child was born in the third trimester group. The diagnosis was cerebral palsy and was not considered to be related to the mother's illness.

Statistics obtained reveal that 87 per cent of the babies born of mothers having German measles during the first trimester were abnormal. No abnormalities developed in the third trimester.

CYCLAINE (D-109), A NEW LOCAL ANESTHETIC AGENT. *R. M. Wylde, M.D. (by invitation), D. M. Waters, M.D. (by invitation) and O. S. Orth, M.D., Madison, Wisconsin.* (From the Departments of Anesthesiology and Pharmacology, University of Wisconsin.)

Cyclaine (D-109) is 1-cyclohexylamino-2 propylbenzoate hydrochloride. Preclinical tests on experimental animals have indicated both a greater anesthetic potency and toxicity but a comparable therapeutic ratio to procaine. The duration of action was equivalent to pontocaine. A preliminary clinical evaluation of cyclaine for spinal analgesia has been made on forty patients.

The site of dural puncture was at lumbar 3–4. Twenty-five to 35 mg. of the drug from a sterile 0.5 per cent solution was used in seven patients. With this preparation onset of analgesia was quite slow, requiring twenty to thirty minutes to develop completely. It then persisted for over two hours.

In thirty-three patients 20 to 50 mg. was administered in a 1 per cent solution of spinal fluid. With this alteration analgesia occurred within sixty seconds and motor paralysis within three to six minutes. Analgesia lasted two hours or longer. The blood pressure declined comparable to the response to other agents, and treatment was similar. Pulse rates also declined. There was slow localization of the level of analgesia. A progressive paralysis of the upper thoracic segments occurred in a patient placed in the Trendelenburg position fifteen minutes after administration of the drug. No serious complications were observed.

Operations which have been performed include inguinal herniorrhaphy, hemorrhoidectomy, vaginal hysterectomy, transurethral prostatic resection, excision of anal fissure, fulguration of bladder tumor, resection of carcinomas of the sigmoid and cecum, cholecystectomy, gastrostomy and appendectomy.

MUSCULAR SYMPTOMS OF ALLERGIC ORIGIN. *Theron G. Randolph, M.D., Chicago, Illinois.*

Allergic muscle symptoms were described by Rowe as part of the clinical picture of "allergic toxemia," more recently reviewed by the writer as the fatigue syndrome of allergic origin. This clinical reaction is usually due to masked food allergy, a concept of food sensitization described by Rinkel which aids in explaining the chronic, smoldering clinical reactions commonly resulting from the oft-repeated ingestion of allergenic foods. Such a mechanism accounts for the fact that patients are rarely able to detect sensitivity to the most important foods such as corn, wheat, milk and eggs because symptoms are usually improved temporarily following the ingestion of a masked food allergen, becoming worse several hours later, particularly during the night or on arising in the morning.

Generalized muscle symptoms consists of aching, lameness, stiffness and soreness. Localized reactions involve the muscles of the nuchal region, particularly the trapezius and the sternocleidomastoid, either unilaterally or bilaterally, and are commonly associated with allergic headaches. Attacks characterized by tightness, tenseness, pulling, drawing or "knotty" sensations in these muscles have been induced experimentally after the test feeding of allergenic foods. Increased tonus and tenderness of the involved muscles may often be demonstrated by palpation. Acute "wry neck" has also been observed under the same circumstances.

The heavy muscles of the lower back may react similarly, giving rise to the complaint of backache. Tightness, "knotty" sensations and localized pain have been observed less frequently in the hamstrings, gastrocnemius, intercostals and the muscles about the shoulder girdle. These muscle symptoms are improved by massage and have been observed to subside with the elimination of specific food allergens.

EFFECT OF PENICILLIN ON THE BLOOD CLOTTING MECHANISM. *R. E. Dolkart, M.D., B. Halpern, M.S., M. Larkin, B.A. and Geza de Takats, M.D., Chicago, Illinois.*

The widespread use of penicillin in a variety of clinical conditions makes any effect of penicillin on the clotting activity of blood of considerable importance. Because of the conflicting reports and the frequent occasions in which penicillin may be used in the presence of altered clotting mechanisms, further studies seemed appropriate.

Penicillin was administered to normal subjects and clotting activity studied by the heparin tolerance test and prothrombin time. The heparin tolerance curve was analyzed and classified into group and heparin reactor group response.

The group heparin tolerance curve and prothrombin time was not significantly altered by penicillin. The heparin reactor groups, hypo-, normo- and hyperreactors, showed a change of borderline statistical significance after penicillin, but still remained within the normal limits of the analyzed group heparin curve.

ADMINISTRATION OF MASSIVE DOSES OF VITAMIN P. HESPERIDIN METHYL CHALCONE. *W. R. Kirtley, M.D.* and *F. B. Peck, M.D., Indianapolis, Indiana.* (From the Lilly Laboratories of Clinical Research, Indianapolis General Hospital.)

The clinical effect of vitamin P substances has been controversial and information has been based largely on observations of the petechial index as determined by one of the positive or negative pressure methods. These methods at best are but crude approximations, as there are several known factors which influence the results. Little is known about the absorption, utilization and excretion of vitamin P. The bulk of animal and clinical studies supports the contention that these flavones do have a definite influence on capillary permeability as distinguished from the capillary fragility of scurvy which responds to ascorbic acid.

Hesperidin chalcone has been identified as the unstable, water-soluble, yellow pigment from crude orange hesperidin which on methylation is stabilized without affecting its vitamin P activity. Since some of the conflicting reports may be due to inadequate dosage or lack of an appropriate test method, repeated observations were made of the blood concentration before and after constriction in cases in which capillary permeability was presumably affected. Criteria of effect were the total protein, albumin and globulin, hemoglobin, erythrocyte count, hematocrit and modified Gothlin's test. Simultaneously the urinary excretion of hesperidin methyl chalcone was measured by the colorimetric borocitric method.

The findings in general indicate that the changes in concentration of blood proteins, erythrocytes, hemoglobin, hematocrit and petechial index are too variable to be statistically significant. As much as 15 Gm. daily have been administered without any evidence of toxic effect. Excretion rates were elevated above the levels of controls but did not show any quantitative relationship to the amounts administered. It is suggested that the flavone may not be quantitatively absorbed, that it undergoes changes in the body into substances incapable of reacting in the borocitric test or that large doses may induce tachyphylaxis.

EFFECT OF INTRAVENOUS ADMINISTRATION OF NICOTINIC ACID ON BLOOD BILIRUBIN. *W. D. Gambill, M.D., B. D. Rosenak, M.D., J. E. Fisher, M.D.* and *R. H. Moser, M.D.* (*introduced by K. G. Kohlstaedt, M.D.*), *Indianapolis, Indiana.* (From the Gastrointestinal Clinic of the Indianapolis City Hospital.)

Marfori, Stefanini and Barmante have reported that following the intravenous injection of nicotinic acid there is a rise of blood bilirubin. They have attempted to adapt this observation to the study of the excretory function of the liver and have suggested that it may constitute an endogenous bilirubin tolerance test. The normal bilirubin curve following the injection of nicotinic acid consists of an initial rise of blood bilirubin with a gradual return to normal over an eight-hour period. We have confirmed this observation in eleven normal individuals.

Twenty-one patients with a variety of liver diseases were studied. Four distinct types of bilirubin curves were obtained. No type of curve was typical of any specific liver disease. In five cases of extrahepatic biliary obstruction no diagnostic type of curve was demonstrated. As a test of liver function it was found the bilirubin curve did not parallel other accepted liver function tests.

STUDIES ON DERMAL HYPERSENSITIVITY IN HUMAN BRUCELLOSIS. *A. I. Braude, M.D., W. H. Hall, M.D.* and *W. W. Spink, M.D., Minneapolis, Minnesota.* (From the Division of Internal Medicine, University of Minnesota Medical School.)

Four Brucella antigens, consisting of a purified protein, a carbohydrate haptene, a protein-nucleate (brucellergen) and the heat-killed organisms, were used to study dermal hypersensitivity in 174 individuals, eighteen of whom had bacteriologically proved brucellosis. The advantage of using four antigens instead of one to detect hypersensitivity is indicated by the fact that in 45 per cent of those with hypersensitivity at least one of the four skin tests was negative.

Agglutinins for Brucella were demonstrated in sixty-five persons, of whom 94 per cent had dermal sensitivity for one or more of the antigens. Dermal hypersensitivity was present in 42 per cent of sixty-nine persons having negative agglutination tests. Of thirty persons with no symptoms, no agglutinins, negative blood cultures and no history of exposure five (or 17 per cent) demonstrated hypersensitivity by the four-test method.

Active infection was demonstrated in fifteen of sixty-two persons with positive agglutinins and positive skin tests. In two cases of Brucella endocarditis the carbohydrate test alone was positive until clinical improvement occurred when dermal sensitivity to the other three agents developed. The carbohydrate haptene is unique also in that it produces an immediate erythema and wheal, can be suppressed by benadryl and readily induces the production of agglutinins. Sensitivity to this antigen can be passively transferred. The other antigens produce a delayed reaction. Areas in which any of these antigens provoked inflammation were occasionally reactivated months later upon the exacerbation of symptoms, recurrence of bacteremia or reapplication of skin tests. Violent local reactions with necrosis occurred in 9 per cent of the brucellergen, 4 per cent of the purified protein, 1 per cent of the vaccine and none of the carbohydrate tests. Brucellergen appeared to elicit the greatest number of false positive reactions.

The intensity of the local reaction could be correlated with the titre of agglutinins. Interesting variations in intensity of reaction occur with the stage of the disease of bacteriologically proved cases. The tests have been of doubtful value from a diagnostic viewpoint.

ARTERIOGRAPHY IN THE EVALUATION OF ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE. *R. G. Smith, M.D.* and *D. A. Campbell, M.D., Eloise, Michigan.* (From the Department of Surgery, Wayne County General Hospital and Infirmary.)

In a recent study of vascular insufficiency due to arteriosclerosis the usual tests were employed. These included (1) skin and muscle temperatures and the response to autonomic blockade. (2) electrical resistance of the skin, (3) biopsy of ulcers and (4) the common tests of function that determine alteration in color, intermittent claudication and resting pain. All of these and other tests indicate to some extent the ability of the blood to reach the undernourished tissues of the leg and foot. But these methods are indirect and the information furnished by them may be incomplete or misleading. To these tests we have added arteriography, which appears to be a more direct approach to the estimation of the type and extent of the pathologic changes which have occurred in the arterial system.

The arteriograms of one hundred cases have been studied and classified according to (1) the location and extent of complete obstruction, (2) irregularities of the lumen and (3) the development of collateral circulation.

This method of examination has been carried out by the intern and resident staff and 75 per cent have been satisfactory from a roentgenographic standpoint. Few complications have been noted, the most important of which has been a mild, transient peripheral neuritis in cases in which an extravascular injection had been made. An occasional hematoma developed at the site of injection.

The classification we have adopted has been used as a basis of selection for suitable candidates for lower leg amputation. In addition, though the classification has been used in only a small number undergoing sympathectomy, it appears that it will be helpful in the selection of patients for this operation.

PLEUROPULMONARY MANIFESTATIONS OF AMEBIASIS. *H. T. Langston, M.D.* (*Introduced by W. G. Maddock*), *Chicago, Illinois.*

During the past year, ten cases of pleural or pulmonary disease due to amebae have been recognized on the Thoracic Surgery Service at Veterans Administration Hospital, Hines, Ill. The patients were all veterans, but not all of them had seen service in parts of the world where infestation is common. A history of dysentery was recalled by most of them, but known amebic dysentery was not recalled by any of them. They presented themselves with histories and clinical findings resembling those of the common types of pleuropulmonary diseases.

Following the thought of the literature in general, we accept an hepatic abscess as the basic pathologic entity responsible for most of these manifestations, except the isolated lung abscess which may well be embolic. The five

types of lesions described by Ochsner and DeBakey are amplified by us to include the hepatic abscess which ruptures into the subdiaphragmatic space and does not transgress the muscular barrier of the diaphragm.

Demonstration of the organism is difficult from the discharges of these cases (sputum or aspirated fluid) because it represents essentially the liquid material from the hepatic abscess and, therefore, conforms to the usual experience in this regard. The diagnosis in our series of cases was made essentially on the basis of unequivocal response to emetine.

Amebic etiology should be suspected in the differential diagnosis of pleuropulmonary disease when: (1) The clinical course is not typical of the more common entities with which it may be confused. (2) The sputum or aspirated fluid has the appearance of "tomato catsup" or "anchovy sauce," etc. (3) A subdiaphragmatic disorder is present without significant antecedent history of suppurative abdominal disease.

From our experience with these ten patients it is our opinion that pleural or pulmonary amebic disease differs from other types of pleural or pulmonary disease in the following points: (1) Dissemination of the disease by bronchogenic route, even in the presence of copious sputum, is not a significant danger. (2) Communication of a pleural or subdiaphragmatic abscess with the bronchial tree does not necessarily imply the presence of superimposed pyogenic infection.

Since in all instances the response to antiamebic therapy was unequivocal, often even dramatic, non-surgical management is the treatment of choice. Aspiration of liquid accumulations is indicated for relief of symptoms or to expedite recovery, but open drainage should be reserved for control of non-amebic complications.

Evaluation of the Esophageal Electrocardiogram in the Diagnosis of Healed Posterior Myocardial Infarction.

H. B. Burchell, M.D., Rochester, Minnesota. (From the Division of Medicine, Mayo Clinic.)

Esophageal electrocardiograms are easily obtained. The use of small but heavy electrodes with thin flexible lead wires, together with a direct writing electrocardiographic machine, has facilitated the recording of them. A study of the value of such electrocardiograms in the diagnosis of posterior myocardial scars (previous infarctions) has been carried out in a series of fifty cases. The fifty cases comprised (1) persons with known previous infarction with and without diagnostic electrocardiographic sequelae, (2) persons with lengthened Q waves in lead III with and without angina pectoris, (3) a few persons with right bundle-branch block with suspected infarction and (4) several patients having anginal pain with the "electrocardiographically vertical" variant of the left ventricular strain pattern. The esophageal electrocardiogram at the ventricular level has shown great variability. In about 10 per cent of cases it retains the form characteristically seen at esophageal levels. When such a form is not present, the electrocardiogram usually simulates the configuration of the left leg unipolar lead, in both "electrocardiographically vertical" hearts or "transverse" hearts. The latter lead (V_F or aV_F) usually is of greater help in evaluation of the significance of prolonged Q waves in derivation III than are esophageal leads. Changes in the esophageal lead that have been most distinctive when myocardial infarction has occurred have been widening and splintering of the initial downward wave and a splintered downward deflection not followed by an R wave. In only one case has a Q wave followed by elevated RT segment been observed. The T wave direction appears to vary independently and has given no help in diagnosis. It appears that an esophageal electrode often continues to be influenced by cavity potential, even when the auricular complex shows no intrinsic type deflection, hence the records obtained usually are not the immediate counterparts of a direct lead from the diaphragmatic area of the ventricle. With the use of the electrodes described, extracardiac potentials produce marked aberrations in the tracings in only a few patients.

Studies on Vasomotor Tone in Hypertension. Effect of Tetraethylammonium on Blood Flow in the Extremities of Normal and Hypertensive Subjects.

H. J. Kowalski, M.D. (by invitation), S. W. Hoobler, M.D., S. D. Malton, M.D. (by invitation), W. G. Pain, M.D. (by invitation), R. H. Lyons, M.D., G. K. Moe, M.D. and *J. T. Manning, M.D. (by invitation), Ann Arbor, Michigan.* (From the University of Michigan.)

It is generally agreed that the primary fault in the hypertensive state is an increase in total

peripheral vascular resistance. It has also been shown that there is an increased resistance to blood flow in the extremities in hypertension. The degree to which this elevated resistance is maintained by increased sympathetic tone of preganglionic origin can be estimated by means of the autonomic blocking agent, tetraethylammonium. An increase in blood flow to an extremity following parenteral administration of the drug is associated with a decrease in neurogenic vasoconstrictor tone, and the magnitude of the response is roughly proportional to the initial level of vasomotor tone. Thus, in the feet where vasomotor tone is at a maximum, increases in blood flow after tetraethylammonium are greatest. When vasoconstrictor tone is decreased by warming the body, the response to the drug is lessened. When vasoconstrictor tone is abolished by sympathectomy, the drug no longer increases blood flow.

Consequently, if initial levels of blood flow in hypertensive and normotensive subjects were similar, administration of tetraethylammonium would produce greater increases in blood flow in the former if the increased tone were of sympathetic origin. Response of blood flow to tetraethylammonium in the forearm and in the foot was determined by means of a venous occlusion plethysmograph in twenty hypertensive and twenty-four normotensive patients.

The mean initial blood flow in the foot was 1.7 cc. per 100 cc. of limb per minute for the hypertensives and 2.0 cc. for the normotensive group. Because of wide individual variations, this difference was not considered to be significant. After intravenous administration of 6 mg. per Kg. of tetraethylammonium, blood flow in both the hypertensive and normotensive subjects increased on the average to 4.4 times the resting levels.

The hypertensive group showed a mean resting flow in the forearm of 3.3 cc. per 100 cc. of limb per minute and the normotensive group showed a mean forearm resting flow of 2.9 cc. per 100 cc. of limb per minute, with an average increase to 1.32 and 1.34 times the resting levels after tetraethylammonium, respectively.

The differences were not considered significant and it is therefore concluded that in the extremities of the hypertensive subjects studied there were no alterations in vasomotor tone of preganglionic autonomic origin.

VASCULAR COMPLICATIONS INCIDENT TO LUMBODORSAL SYMPATHECTOMY. *R. D. Taylor, M.D., A. C. Corcoran, M.D.* and *I. H. Page, M.D., Cleveland, Ohio.* (From the Research Division, Cleveland Clinic Foundation.)

Lumbodorsal sympathectomy is an accepted treatment in some phases of essential hypertension. The frequency of postoperative morbidity and mortality due to vascular causes in such patients is not widely recognized. The incidence of such complications among one hundred hypertensive persons operated upon was surprisingly great. Seventy-nine of these patients had essential hypertension and twenty-one of them were in the malignant phase. The average age was 37.6 years (range twelve to fifty-three years).

Fifteen patients suffered from some form of vascular decompensation in the immediate postoperative period. Among those, three patients with malignant and one with essential hypertension died during or immediately after operation. One patient sustained a myocardial infarction and died after a second attack six weeks later. Acute left ventricular failure and auricular fibrillation occurred on two occasions. The cardiac complications may result from acute coronary insufficiency. One patient developed the signs and symptoms of renal failure, possibly because of the sudden marked reduction of arterial pressure. The remaining seven patients gave evidence of cerebral vascular changes. Minor episodes were attributed to minimal cerebral thrombosis. Major episodes with disorientation or actual psychosis were thought to be due to multiple small thrombi. Of the one hundred patients operated upon, four died presumably directly as a result of operation and eleven showed serious disability.

These observations serve to emphasize that lumbodorsal sympathectomy should not be undertaken lightly and that the risk involved should be recognized.

EFFECT OF SERUM PROTEIN DEPLETION ON WATER AND SALT EXCRETION AND SENSITIVITY TO PITUITRIN. *J. S. Schweppe, M.D.* and *S. Freeman, Ph.D., M.D.* (*Introduced by Howard A. Lindberg, M.D.*), *Chicago, Illinois.*

Three dogs were depleted of their serum proteins by a combination of a 4 per cent protein diet and plasmapheresis three to five times per

week. One dog remained as a control throughout the period. Serum protein depletion had the following effects in the dogs studied: (1) The time required to excrete 50 per cent of ingested water increased in all dogs following depletion. This was statistically significant only in one animal. (2) Protein depletion had no effect on the daily twenty-four-hour excretion of chloride. (3) Protein depletion did not appear to alter the twenty-four-hour excretion of chloride after the oral administration of an 0.85 per cent saline solution. (4) During depletion extracellular fluid volume increased slightly in two dogs. (5) The glomerular filtration rate was reduced in all protein depleted dogs. (6) The urinary suppression produced by pituitrin increased markedly in one dog and only slightly in two others. (7) Desoxycorticosterone acetate in 2 mg./Kg. dosage reduced sodium excretion in all dogs, but had no significant effect on the blood sodium, potassium or chloride levels. Water excretion was not appreciably changed except in one animal which showed a marked suppression. (8) No gross edema or ascitic fluid was present on autopsy. (9) No significant pathologic change was found which could explain the results obtained.

SEROLOGIC TEST FOR STAPHYLOCOCCAL INFECTIONS. *Charles H. Rammelkamp, M.D., Cleveland, Ohio.* (From the Departments of Preventive Medicine and Medicine, School of Medicine, Western Reserve University.)

Association of potential pathogenicity of staphylococci with the production of an extracellular substance which clots plasma has been widely recognized. In spite of this correlation little is known concerning the rôle of staphylococcal coagulase in the disease process. The existence of antibodies which inhibit the coagulase reaction has not been demonstrated, possibly due to inadequacies of the several technics employed. In reinvestigating this problem, therefore, it was first necessary to devise a serologic test whereby the factors entering into the coagulase reaction could be controlled. Fraction I of the plasma proteins was employed as the indicator system. Staphylococcal coagulase was obtained by growing Staphylococcus aureus in tryptose phosphate broth containing 1 per cent human plasma following which the medium was passed through a Seitz filter. A unit was defined as three times the minimum concentration required to cause the appearance of fibrin in a standard fibrinogen-activator preparation. In determining the neutralizing effect of a serum, a unit of coagulase was placed in contact for a period of ninety minutes with varying dilutions of the serum to be tested, following which a constant amount of substrate, fibrinogen, was added. After three hours incubation the tubes were examined for inhibition of the formation of visible fibrin.

The aforementioned serologic test was employed in a study of sera collected from normal subjects, from patients with staphylococcal infections and from monkeys immunized with cell-free coagulase. The coagulase inhibitory effect of sera from normal subjects varied considerably; many sera exhibited no anticoagulase effect while a few completely inhibited the reaction in dilutions of 1:500 or greater. Acute and convalescent phase sera obtained from patients with staphylococcal infections revealed an increase in the anticoagulase titer in the later blood specimens. These results suggested that coagulase was antigenic. Confirmation was obtained by the demonstration of a rising titer of anticoagulase in the sera of monkeys following immunization with cell-free coagulase. The rôle of this antibody, as well as that of coagulase itself, in the mechanism of infections remains to be established.

PRECORDIAL AND UNIPOLAR EXTREMITY ELECTROCARDIOGRAMS IN FIFTY YOUNG NORMAL MALE ADULTS. *P. H. Noth, M.D.* and (*by invitation*) *H. A. Klein, M.D., Detroit, Michigan.*

The Wilson precordial leads (V_3R, V_1–V_6) and Goldberger unipolar extremity leads of fifty young male adults whose hearts were normal by physical and roentgenographic examination were analyzed. The durations of Q, R and S were determined with a Cambridge measuring device. Isolated findings of clinical importance are reported here.

Findings in Precordial Leads. The maximal duration of R (or R–Q) was 0.04 seconds or longer in seven patients, in one of whom it measured 0.045 seconds. Such values are usually considered suggestive of left ventricular hypertrophy. The average of the durations of R (or R–Q) maximal for each patient was 0.034 seconds, which is identical with the value

found for this measurement in sixty-seven pathologically proved cases of left ventricular hypertrophy.

The maximal duration of the QRS complex was 0.114 seconds; for eight subjects it was 0.11 seconds or more and for nineteen subjects, 0.105 seconds or more.

In V_3R, QS deflections occurred in three cases, but otherwise were absent except in one instance in V_1. Q deflections were not present in leads V_3R, V_1, V_2 or V_3. The tallest R in V_3R measured 6.0 mm., in V_1, 9.0 mm. The duration of R in V_3R varied between 0.001 and 0.031 seconds, averaging 0.017 seconds. In both V_1 and V_2 the maximal values for the duration of R were 0.033 seconds, the average values 0.020 and 0.023, respectively. The T waves in V_3R were inverted in thirty-five, diphasic in two, isoelectric in five, and upright in eight cases. These findings are of interest chiefly for comparison with those in right ventricular hypertrophy and "strain."

Findings in Goldberger Extremity Leads. Duration from onset to nadir of Q in the thirty-four unipolar leads reflecting purely or predominantly left ventricular potentials varied between 0.006 and 0.021 seconds. The depth of Q in these leads varied between 0.5 and 3.0 mm. never exceeding 23 per cent of the height of the following R wave. Thus a Q wave pattern simulating that associated with myocardial infarction was absent.

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE WESTERN SECTIONAL MEETING
HELD IN SAN FRANCISCO, NOVEMBER 6, 1947

USE OF HEPARIN IN PRE-ECLAMPSIA. *E. W. Page, M.D., San Francisco, California.* (From the Department of Obstetrics and Gynecology, University of California Medical School.)

During pregnancy the maternal blood is in direct contact with the epithelium of the placenta, an organ which is exceedingly rich in thromboplastin. As shown by Gaifami and many others, saline extracts of the human placenta are lethal to animals when injected intravenously. Schneider has identified this lethal factor as thromboplastin, and suggests that it may be responsible for the fibrin deposition and capillary thromboses observed in the eclamptic woman's liver. Should this be true it might be expected that heparin, a thromboplastin antagonist, would alter the course of pre-eclampsia.

Four women with antepartum pre-eclampsia have been heparinized for periods of seventy-two hours, two by continuous intravenous infusion and two by the intermittent injection of 50 mg. of heparin intravenously every three to four hours. In each case the patient was hospitalized for periods of two to five days in order to use each subject as her own control. In two mild cases the hypertension subsided and proteinuria decreased sharply during the period of heparinization. This apparent improvement continued after stopping the heparin treatment, but the disease recurred in a mild form weeks later in one patient at the time of labor. Two patients with severe cases of pre-eclampsia were treated, one at the seventh and one at the eighth month of pregnancy. In the earlier case the only symptoms were marked hypertension and proteinuria and during heparinization there was no improvement in her condition. A week after cessation of heparin therapy the infant died *in utero* and pregnancy was terminated. In the remaining case of severe pre-eclampsia the outstanding symptom was marked epigastric pain and liver tenderness. During the three days of heparin infusion these symptoms disappeared, the hypertension fell from an average of 190/110 to 160/100 and the proteinuria decreased from 3 to 0.4 Gm. per day. Within twelve hours after cessation of heparin, the epigastric pain returned, blood pressure rose to 200/120 and proteinuria increased. Pregnancy was terminated by cesarean section and a living baby was obtained.

These preliminary results suggest that heparin might be a valuable adjunct in the treatment of pre-eclampsia for the prevention or possibly the alleviation of hepatic damage.

STUDIES ON ERYTHROCYTE PROTOPORPHYRIN, PLASMA IRON AND PLASMA COPPER IN NORMAL AND ANEMIC SUBJECTS. *M. M. Wintrobe, M.D.* and *G. E. Cartwright, M.D. (by invitation), C. M. Huguley, M.D.* and *J. Fay, M.D., Salt Lake City, Utah.* (From the Department of Medicine, University of Utah, School of Medicine.)

Values for free erythrocyte protoporphyrin, plasma iron and plasma copper determined in a series of normal adults are presented and analyzed. One or more of these determinations were made in 101 patients with various disturbances in erythropoiesis. In pernicious anemia the erythrocyte protoporphyrin values were normal, the plasma iron normal or elevated and the plasma copper not consistently altered from the normal. In patients with anemia due to a deficiency of iron, the erythrocyte protoporphyrin was found to be high, the plasma iron low and the plasma copper normal or high. Anemia associated with chronic infection was accompanied by a high value for erythrocyte protoprophyrin, a low plasma iron level and increased plasma copper. In nephritis the erythrocyte protoporphyrin was usually elevated, the plasma iron low or normal and the plasma copper variable. Patients with lymphoma and leukemia had a normal or high erythrocyte protoporphyrin, low or normal plasma iron and high plasma copper. In aplastic anemia, plasma iron was elevated. Plumbism was accompanied by high erythrocyte protoporphyrin and normal plasma iron. Myelophthisic anemia was also characterized by a high protoporphyrin content of the erythrocytes. In hemolytic anemia the values were variable. A low plasma copper value was noted in a single patient with hemochromatosis. Thalassemia major was found to be accompanied by a high plasma iron. Mis-

cellaneous diseases including polycythemia, hypothyroidism, multiple myeloma, Laennec's cirrhosis, subacute yellow atrophy of the liver, Banti's syndrome, constitutional hyperbilirubinemia, thalassemia minor and acute prophyria exhibited no abnormal deviations.

ACUTE IDIOPATHIC HYPOPROTHROMBINEMIA. RESPONSE TO MASSIVE DOSES OF SYNTHETIC VITAMIN K. *R. D. Friedlander, M.D., I. K. Heindl, M.D. (by invitation)* and *B. G. Anderson, M.D., San Francisco, California.*

The clinical course and dramatic response to vitamin K are described in the case of a middle aged female with apparent idiopathic hypoprothrombinemia. The prognosis was considered to be very grave due to severe respiratory embarrassment as a result of extensive hemorrhage into the deep and superficial tissues of the neck and base of the tongue. Rapid recovery followed administration of large doses of synthetic vitamin K and whole blood. Evidence of hepatic disease was not demonstrable by the usual tests of liver function. Since the patient had been taking small amounts of salicylates, the influence of this drug on the prothrombin time is discussed.

THROMBOPLASTIN REAGENT OF ENHANCED POTENCY AND ITS SIGNIFICANCE WITH RELATION TO THE THEORY OF THE QUICK PROTHROMBIN TEST. *P. M. Aggeler, M.D., T. B. Leake, A.B. (by invitation)* and *J. Talbot, M.D., San Francisco, California.* (From the Department of Medicine, University of California Medical School.)

Storage of a small quantity of acetone-extracted human or rabbit brain as a thin layer in a glass beaker contained within an evacuated calcium chloride desiccator for periods varying from 47 to 120 days resulted in a marked increase in its thromboplastic potency. Prothrombin times performed with thromboplastin reagent prepared from brains treated in this manner were shorter in normal plasma diluted to 50 per cent of its original concentration than the times obtained with the same plasma in the undiluted state. The results are interpreted as indicating the presence of coagulation-inhibiting substances both in the plasma and in thromboplastin reagents prepared in the usual manner. The results can be explained by the assumption that the increased thromboplastic potency of brains stored in the manner herein described is due to more complete dehydration resulting in relatively greater insolubility of the coagulation inhibitor contained in the brain.

It is proposed that the prothrombin time obtained with thromboplastin reagents prepared in the usual manner is the net result of a reaction among prothrombin, plasma coagulation inhibitor, thromboplastin and a coagulation inhibitor contained in the thromboplastin reagent. With elimination of the latter inhibitor from the reaction, the effect of dilution of prothrombin to 50 per cent of its original strength is overbalanced by the effect of dilution of the plasma coagulation inhibitor thereby resulting in a faster prothrombin time in the diluted plasma.

COMPARATIVE STUDY OF THE EFFECTS OF ADMINISTRATION OF LARGE DOSES OF HORSE SERUM AND HUMAN ALBUMIN TO RABBITS WITH REFERENCE TO FORMED ELEMENTS OF THE BLOOD, PLASMA PROTEIN CONSTITUENTS AND IMMUNOLOGIC CHANGES. *B. V. Jager, M.D.* and *R. J. Nelson, M.D. (by invitation), Salt Lake City, Utah.* (From the Department of Medicine, University of Utah Medical School.)

The clinical and experimental observations that serum sickness may result in pathologic lesions simulating those of periarteritis nodosa and acute rheumatic fever suggest that a study of certain hematologic and immunologic aspects of experimental serum sickness in animals might offer useful information.

One group of ten rabbits was given intravenously a single, large dose of horse serum (mixed antigen); a similar group received a single large dose of human albumin (relatively homogenous antigen) while a third group of equal number served as controls. Specimens of blood for various studies were obtained repeatedly from each group during a seven-week period following injection of a foreign protein.

With the exception of a transient lymphopenia which followed injection of albumin or horse serum, the injection of foreign proteins did not lead to significant changes in the packed red cell volume, total and differential leukocyte counts and the reticulocyte response when compared with the control group.

In spite of inherent difficulties attributable to animal variations the rabbits receiving horse

serum showed a moderate increase in plasma fibrinogen and a delayed rise in total globulin and "gamma globulin" (determined chemically). No significant reduction in serum albumin occurred. By contrast no impressive changes occurred in these protein constituents in the animals receiving human albumin. After injection of antigen, circulating precipitinogen persisted much longer and precipitins appeared earlier in the group receiving horse serum than the one receiving human albumin. Antibodies to a globulin fraction of horse serum seemed to develop earlier than antibodies to horse serum albumin.

The total quantitative serum hemolytic complement decreased following administration of horse serum but not after injection of human albumin.

CORRELATION OF LIVER STRUCTURE AND FUNCTION. *L. W. Kinsell, M.D., H. A. Weiss, M.D., G. Michaels, M.D. (by invitation), J. Shaver, M.D.* and *H. Barton, M.D., Oakland, California.* (From the Department of Medicine, University of California Medical School and the U. S. Naval Hospital.)

Serial liver biopsies have been performed on individuals with acute and chronic liver damage. These patients have been studied simultaneously from the standpoint of liver function as manifested by standard liver function tests as well as by certain other procedures.

It has been found that, in general, acuteness of liver damage is manifested in the biopsy section by phagocytic cell infiltration and that this is usually correlated with the cephalin flocculation test and that chronic, long-standing changes may be correlated with abnormalities of the bromsulfthalein test and with decreased glycogen storage.

COMPARISON OF CHEMICAL DETERMINATION OF SERUM ALBUMIN CONCENTRATION WITH CORRESPONDING ELECTROPHORETIC PATTERNS. *T. B. Schwartz, M.D. (introduced by B. V. Jager, M.D.), Salt Lake City, Utah.* (From the Department of Medicine, University of Utah Medical School.)

Numerous observers have shown that the commonly used sodium sulfate precipitation method of Howe for the determination of serum albumin concentration gives false high values when compared with those obtained by electrophoresis. In view of the obvious need for a simple, easily executed clinical procedure for estimating albumin concentration in normal and pathologic sera, the results obtained by three precipitation technics were compared with values obtained by electrophoresis. All four procedures were carried out on aliquots of individual samples of both normal and abnormal sera, the albumin concentration ranging from 17 to 64 per cent in the series of sera tested.

As noted by others the Howe method (21.5 per cent sodium sulfate) yielded serum albumin concentrations that were 4 to 20 per cent higher than those determined electrophoretically. The methanol precipitation procedure described by Pillemer was found to be technically difficult to control and, in pathologic sera, gave results which were consistently lower than the electrophoretic values. Precipitation of serum globulin by saturated magnesium sulfate (Popjak and McCarthy) was found to be a reliable and relatively accurate method for serum protein partition, yielding serum albumin values which correlated closely with those obtained by electrophoresis.

EFFECT OF 2,3-DIMERCAPTOPROPANOL (BAL) ON TOXICITY AND EXCRETION OF GOLD. *W. C. Kuzell, M.D., P. L. Pillsbury, M.D.* and *S. A. Gellert, B.A., San Francisco, California.* (From the Departments of Pharmacology and Therapeutics and of Medicine, Stanford University School of Medicine.)

Recent clinical observations have shown that 2,3-dimercaptopropanol (BAL) is of value in counteracting the toxic manifestations of gold salts used in the treatment of patients with rheumatoid arthritis. This report presents the results with BAL in protecting white rats against toxic doses of gold sodium thiosulfate and gold chloride and on urinary excretion of gold in rabbits. BAL protects rats against lethal doses of gold sodium thiosulfate given intramuscularly but not against lethal doses of gold chloride given intraperitoneally. Gold chloride is not readily absorbed when given intramuscularly due presumably to severe local tissue destruction. BAL facilitates excretion of both gold sodium thiosulfate and gold chloride given in-

travenously to rabbits in non-lethal doses. *In vitro* BAL reacts readily with gold sodium thiosulfate to produce a golden yellow precipitate, and with gold chloride to produce a russet brown precipitate thus indicating a high affinity of the thiol groups in BAL for gold, but presumably some tissue-soluble complex is the basis for the antagonistic action in living tissues. The experimental results obtained support the beneficial effects of BAL in clinical manifestations of gold toxicity.

EXCRETION OF UROBILINOGEN IN THE URINE IN PATIENTS SUFFERING FROM CARDIOVASCULAR DISEASES. *F. S. Focht, M.D.* and *H. T. Hanson, M.D.* (*introduced by H. H. Hecht, M.D.*), *Salt Lake City, Utah.* (From the Department of Medicine, University of Utah, School of Medicine.)

Watson and his associates have recently reported that in patients suffering from myocardial infarction, semiquantitative measurements of urobilinogen excreted during a two-hour period revealed increased values for several days following the acute episode. The degree of increment was believed to correlate with the clinical course in such patients.

Repeated tests were performed on a large number of patients suffering from a variety of diseases. The present report deals only with the results obtained in ten instances of myocardial infarction, eleven examples of peripheral vascular thrombosis and emboli and eight patients who were in congestive heart failure not secondary to myocardial infarction.

In congestive heart failure either no rise in urobilinogen excretion in the urine was observed or high values were found on the day of admission, these receding toward normal during the next few days of intensive treatment. In all but one of the patients suffering from myocardial infarction, excretion titers above normal were observed for at least one day. In contrast to patients in congestive heart failure the average maximum excretion occurred on the fourth day following onset of clinical symptoms. It appeared that lower levels were obtained in patients in whom the clinical course and serial electrocardiograms suggested small, non-penetrating infarcts. Peripheral thrombi and emboli were invariably followed by a rise in urine urobilinogen occurring on the average during the first or second day following the onset of clinical signs.

It is pointed out that simple determination of the excretion of urobilinogen in the urine from samples collected during a two-hour period provides another method with which to follow and gauge patients with acute myocardial infarction. It is of no value in differentiating chest pains caused by pulmonary emboli or dissecting aneurysm from those secondary to occlusion of a coronary artery.

PRIMARY CARCINOMA OF THE LUNG. CYTOLOGIC STUDY OF SPUTUM AND BRONCHIAL SECRETIONS. *S. M. Farber, M.D., M. A. Benioff, M.D.* and *G. Tobias, M.D., San Francisco, California.* (From the University of California Tuberculosis Service, San Francisco Hospital.)

A review of the clinical and pathologic material of 200 cases of primary carcinoma of the lung which came to autopsy at the University of California Medical School and the Stanford Medical School revealed that diagnosis was usually made in the late or terminal stages of the disease. Since primary carcinoma of the lung is bronchogenic in origin, a cough productive of sputum is found in the majority of patients. Examination of sputum or of bronchoscopically removed secretions for neoplastic cells has been reported at various times since the published observations of Hampeln in 1887. Recent advances have been made in proper identification of the cellular elements of the bronchial secretions through use of the Papanicalaou and Traut vaginal smear technic. This method gives an extremely high degree of nuclear and cytoplasmic detail.

This paper presents the cytologic criteria for diagnosis of malignant cells found in the sputum and bronchial secretions. Comparison is made with the cellular components in patients with acute and chronic pulmonary diseases and with the normal epithelial cells, cells from the blood stream and the reticuloendothial system. Clinical histories are listed when the cytologic examination of the sputum or bronchial secretions established the diagnosis of primary carcinoma of the lung.

USE OF FIBRIN FOAM IN BRONCHIAL STUMP CLOSURE. *M. F. Kepl, M.D.* and *R. E. Ahlquist, M.D., Spokane, Washington.*

It has been shown by Bailey that final reaction to a large quantity of fibrin foam with

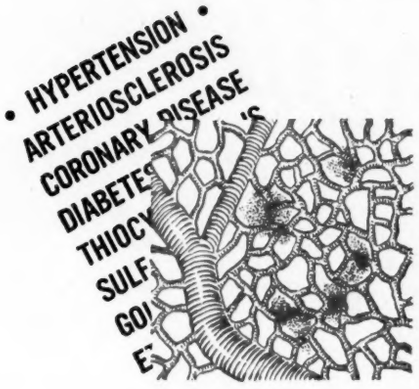
thrombin is less than that to a single black silk suture. After implantation no leukocytic infiltration appears. Fibrin foam is absorbable and controls oozing of tumor beds and cut surfaces of parenchymatous organs.

It is the purpose of this communication to discuss the rationale of the use of fibrin foam as a bronchial plug in the closure of the bronchial stump after lobectomy or pneumonectomy with the anticipation that probably the fibrin foam would act as a scaffolding on which histiocytes and capillary buds would proliferate and hold the bronchial stump, thus preventing the well known phenomenon of "blown bronchus."

A case history is presented in which lobectomy was done for bronchiectasis during which operative procedure it was not possible to cover the bronchial stump with a pleural flap. Fibrin foam, dipped in thrombin, was sutured in place over the closed end of the bronchus which was then irrigated with penicillin-saline solution.

Healing was uneventful. No blown bronchus was evident and the patient returned to work approximately six weeks after the operative procedure. It was believed that the use of fibrin foam in this procedure played a definite role in aiding bronchial stump closure, particularly when the stump could not be covered with pleura.

to reduce risk of vascular accident due to



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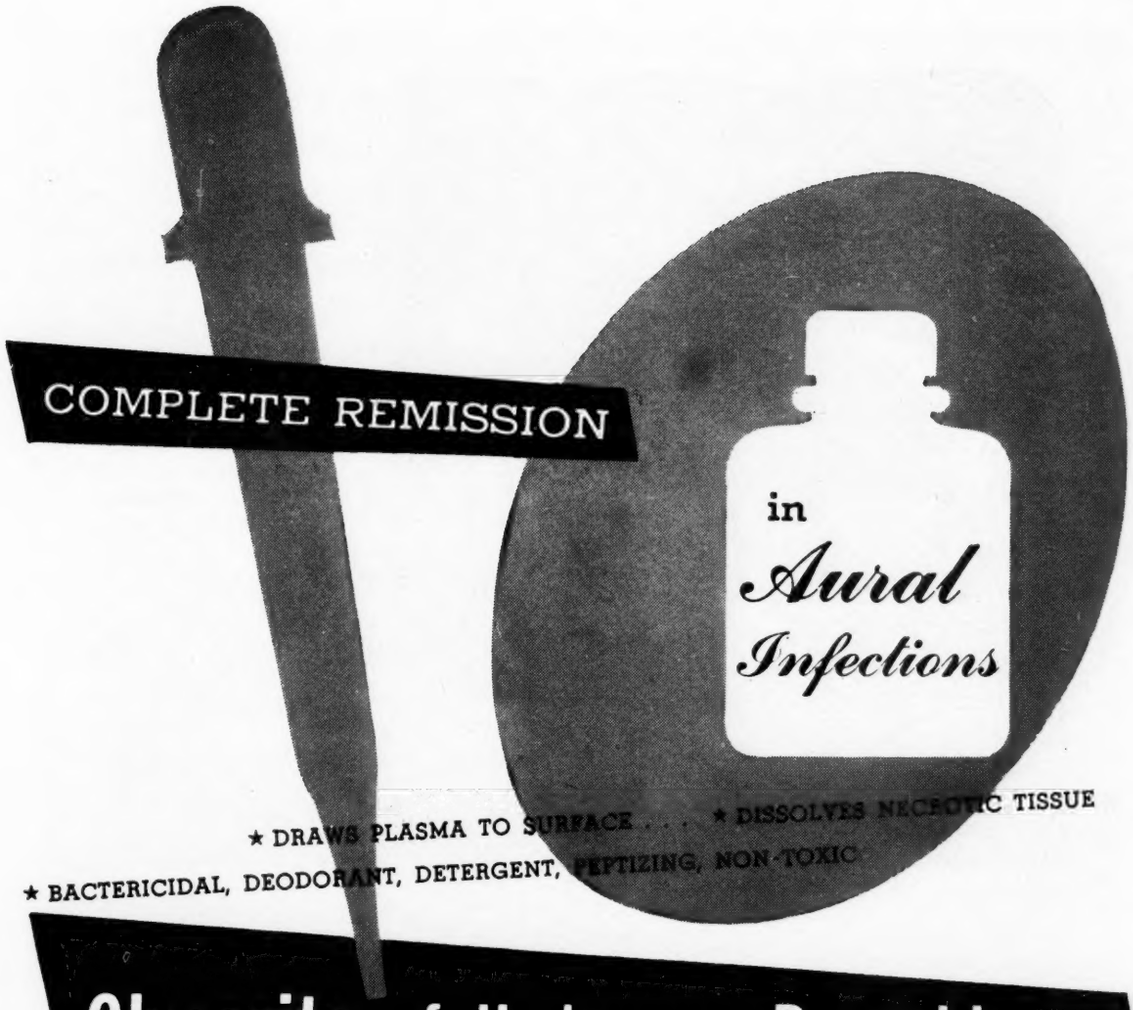

Glycerite of Hydrogen Peroxide ipc
With Carbamide

★ **BIBLIOGRAPHY**

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Literature on request.

Clinical studies concerned with the use of Glycerite of Hydrogen Peroxide in the treatment of chronic purulent otitis media demonstrated seventeen of twenty-nine patients in complete remission in 14 days and the remainder by the 38th day. The patients studied presented conditions existent for periods of 2 weeks to over 40 years. Previous treatment by the usual therapeutic means, including tyrothricin or penicillin, was ineffective in all cases.

Constituents:

Hydrogen Peroxide 1.446%, Urea (Carbamide) 2.554%, 8-Hydroxyquinoline 0.1%.
Dissolved and stabilized in substantially anhydrous glycerol . . . q.s. ad. 30cc.

Available on prescription in one-ounce bottle with dropper.
Administration: One-half dropperful two to four times daily.

International **PHARMACEUTICAL CORPORATION**
132 NEWBURY STREET, BOSTON 16, MASSACHUSETTS

Nutritional adequacy is a fundamental requisite for normal convalescence. LIVER AND YEAST EXTRACT *ARMOUR* is an excellent nutritional adjuvant, not only because of the nutritional factors it contains, but also because of its tonic effect and stimulating action on the appetite. It hastens convalescence and helps overcome lassitude, fatigue and malaise. Furunculosis and inflammatory or ulcerative lesions of the mucous membrane may yield also to Liver and Yeast therapy.

LIVER AND YEAST EXTRACT *ARMOUR* is absorbed rapidly and its physiologic stimulating effect is noted promptly. In this preparation, the yeast has been washed free from gastrointestinal irritating properties. The hydrolyzing and stabilizing processes are so conducted that the often objectionable liver odor and taste are eliminated while the primary and secondary anti-anemic factors as well as the vitamin B complex of both liver and yeast are preserved. It is quite palatable.

LIVER AND YEAST EXTRACT *ARMOUR* is supplied in 8 ounce bottles. The adult dose is two teaspoonfuls twice daily. Larger doses, if indicated, may be given safely. It is best administered in a little milk, water, or fruit juice. When there is a decided tendency toward secondary anemia it may be given in conjunction with some form of iron.

℞ Liver and Yeast Extract Armour

Have confidence in the preparation you prescribe – specify ARMOUR.

ARMOUR Laboratories
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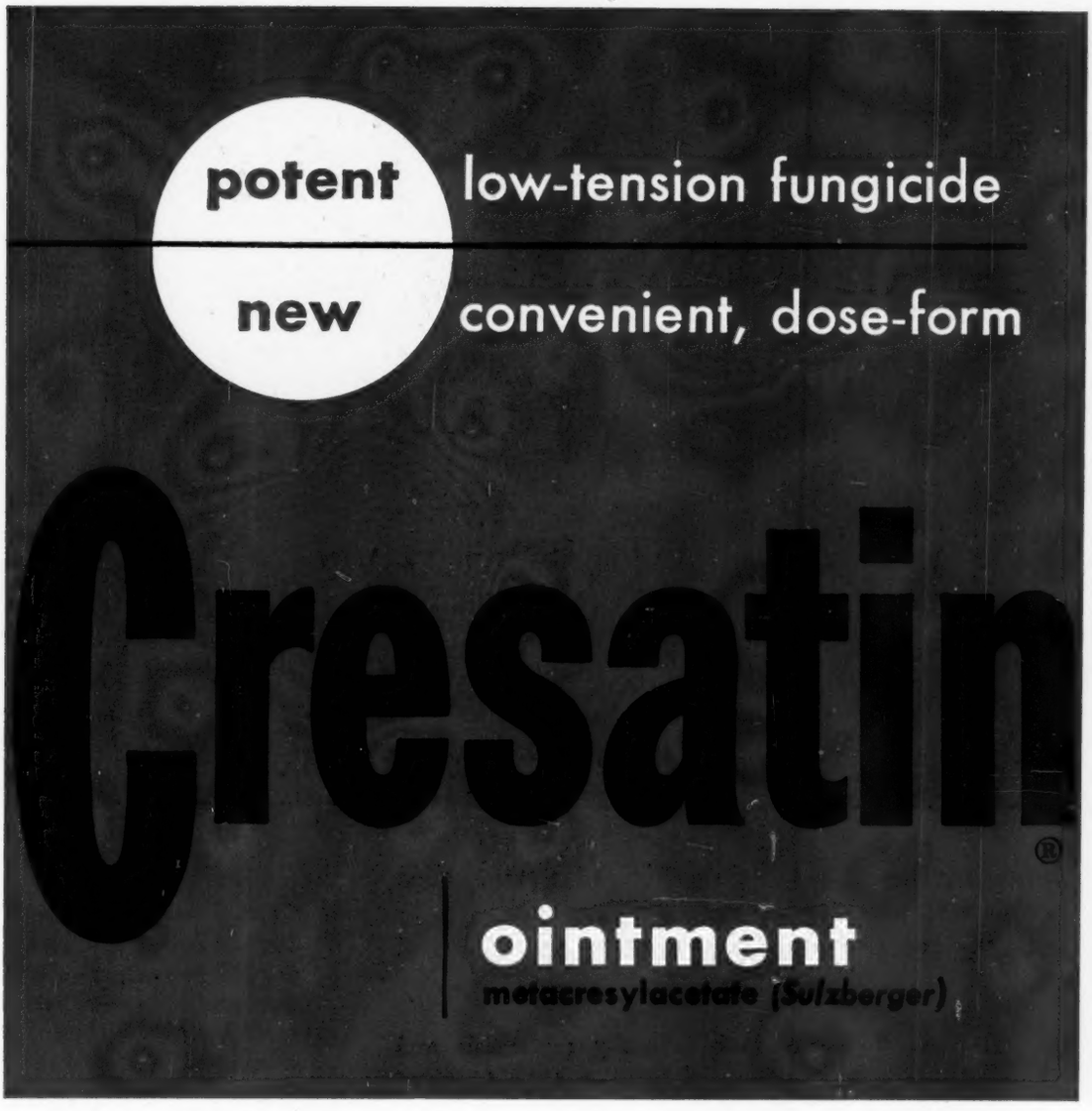
HEADQUARTERS FOR MEDICINALS OF ANIMAL ORIGIN



Low surface tension makes CRESATIN *metacresylacetate* one of the most penetrating and efficient of fungicides for treatment of common mycotic skin infections. It is now available in a specially compounded, clear ointment base, for maximum convenience in treatment of foot ringworm and other dermatophytoses, erythrasma, and tinea circinata, versicolor, and cruris.

CRESATIN Ointment not only exerts high fungicidal efficiency, but is analgesic, antiseptic, and mildly keratolytic as well. Finally, in contrast to its strong fungicidal action, due to volatility and low surface tension, CRESATIN Ointment is relatively and reassuringly nontoxic. Supplied in tubes containing ¼-ounce of CRESATIN *metacresylacetate*, 80%. Sharp & Dohme, Philadelphia 1, Pa.

CRESATIN *ointment*

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Among the advantages provided by this new seal are:

- The round tear-off tab is easily removable and eliminates the necessity of using a knife or other implement to pry up the tab.
- The tight-fitting dust cap with skirt provides protection for the rubber stopper during storage of the vial between injections.

Crystalline Penicillin G Sodium Merck is a highly purified product from which therapeutically inert materials have been virtually eliminated.

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Outstanding advantages of Acnomel's special new vehicle . . .

Acnomel's superior vehicle embodies an entirely new principle in topical acne therapy. To this vehicle—a stable, grease-free, *flesh-tinted hydrosol*—ACNOMEL owes the following important advantages:

1. It is easy to apply smoothly and evenly.
2. Upon application, it dries in a few seconds.
3. Its active ingredients are maintained in intimate and prolonged contact with the affected areas.
4. It removes excess oil from the skin.
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a significant advance, clinical and cosmetic,

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Salyrgan Theophylline

BREON

Supplied: 1 cc and 2 cc ampuls in boxes of 12, 25, 100. Tablets Enteric Coated, Bottles of 100 and 500.

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Salyrgan-Theophylline eliminates both water and sodium. The first injection may cause the patient to lose as much as 10 pounds. "Dry weight" can be achieved promptly and usually maintained with properly spaced injections of Salyrgan-Theophylline.

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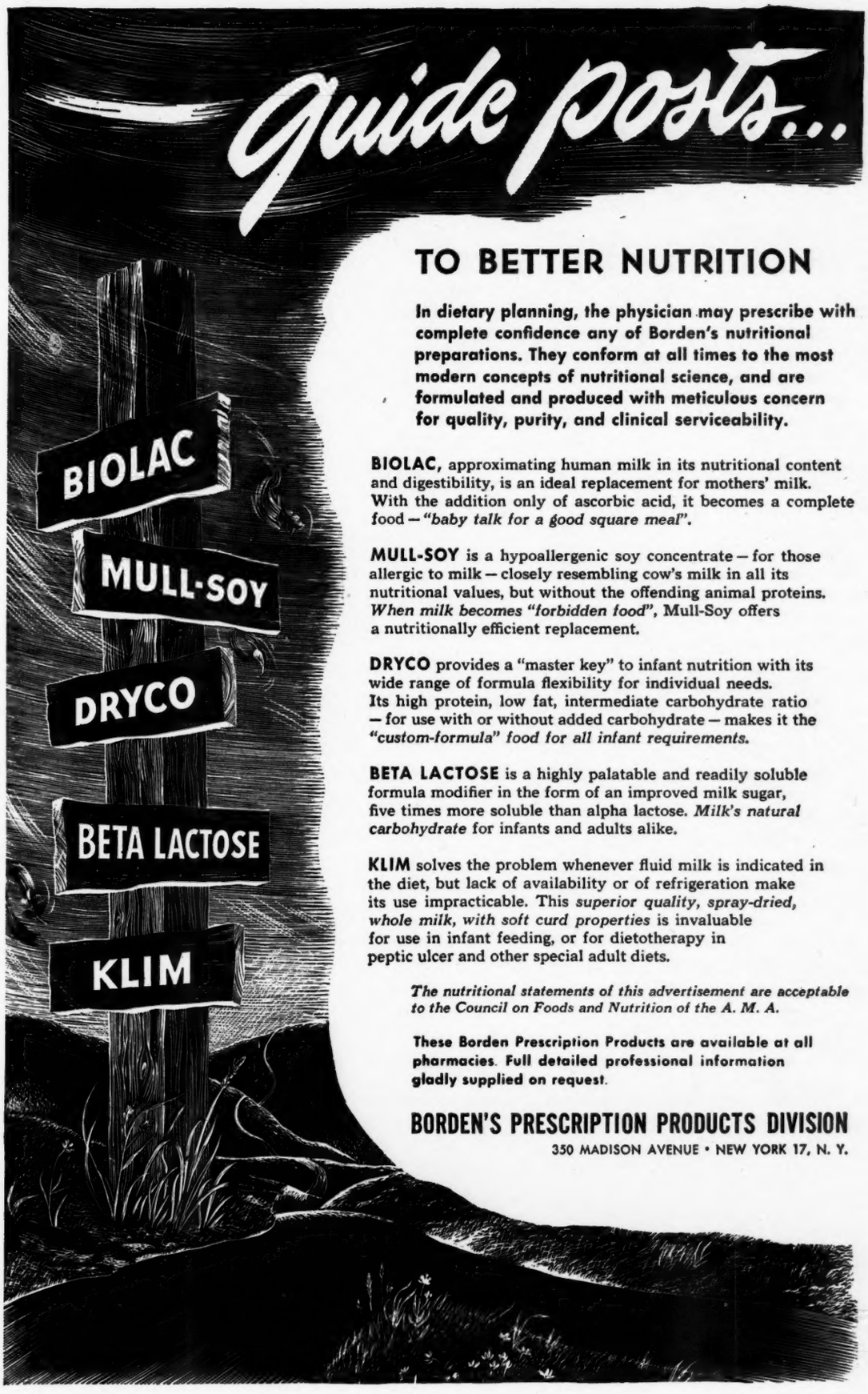

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The nutritional statements of this advertisement are acceptable to the Council on Foods and Nutrition of the A. M. A.

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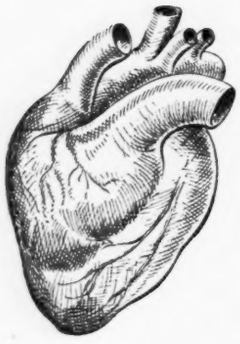

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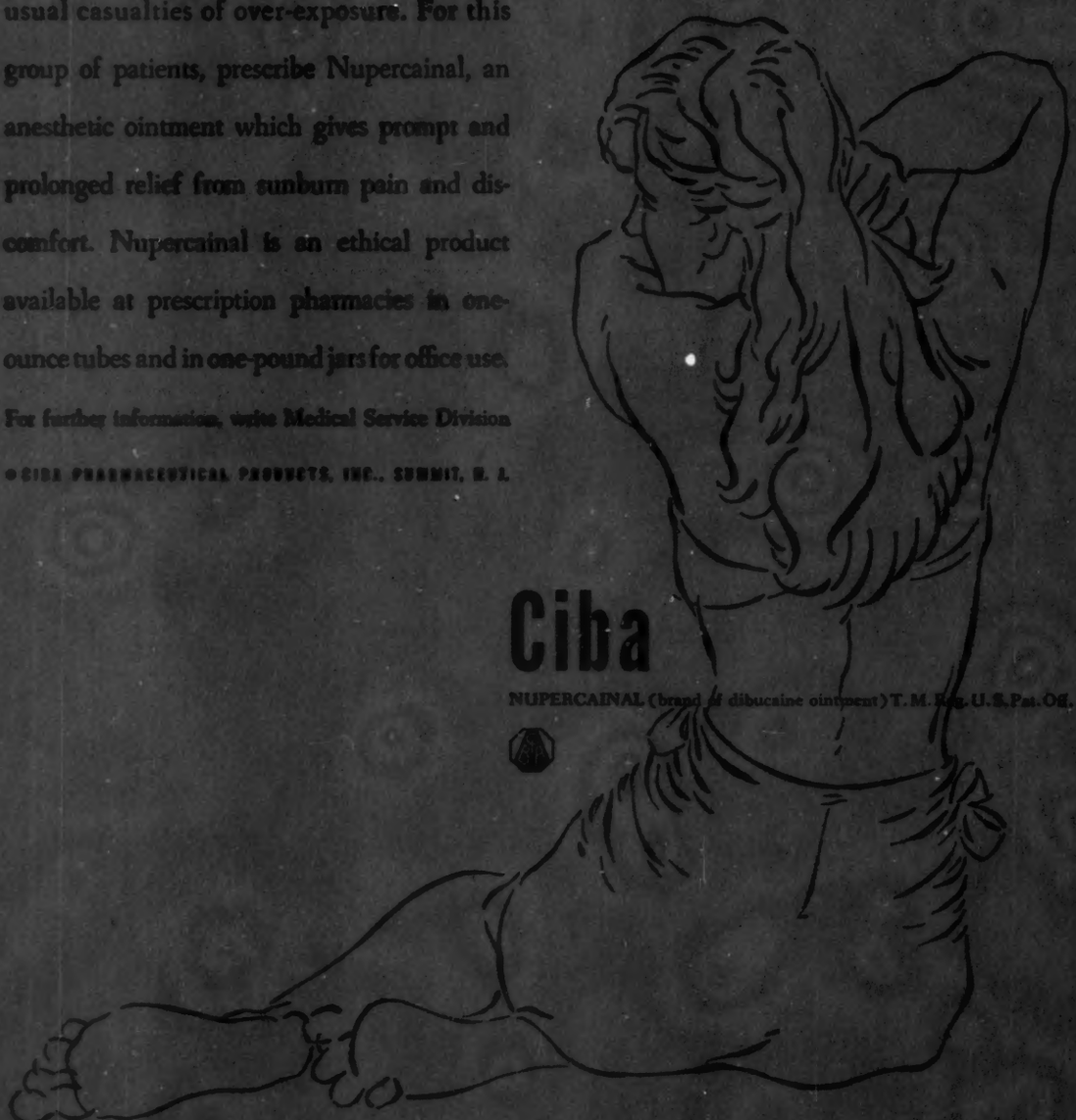

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